TEXTBOOK OF ENDOCRINOLOGY

ENDOCRINOLOGY

by

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Nobel Prize Laureate 1947
Buenos Aires, Argentina

Second Edition

ACTA ENDOCRINOLOGICA INC.
MONTREAL, CANADA

FIRST EDITION

First printing 1947
Second printing 1947
Third printing 1948
Fourth printing 1948
Fifth printing 1948

SECOND EDITION

First printing 1949

PRINTED IN CANADA

CE LIVRE EST DÉDIÉ AUX ÉTUDIANTS
DE
L'UNIVERSITÉ DE MONTRÉAL

PREFACE TO FIRST EDITION

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La Endocrinologia se ocupa del estudio de la acción de las hormonas, en condiciones normales y patológicas, como reguladoras de funciones importantes del organismo. — Las hormonas son sustancias orgánicas producidas especificamente por las glándulas de secreción interna y que una vez descargadas en los liquidos circulantes (medio interno), alcanzan todas las partes del organismo e influyen marcadamente sobre las funciones de determinadas células o sistemas, obrando en pequeñas cantidades y sin contribuir por ellas mismas importantes cantidades de materia o energia. —

Las hormonas regulan importantes procesos quimicos y funcionales del organismo, pudiendo modificar probablemente la marcha de reacciones enzimáticas fundamentales, sin que se haya comprobado que entren a formar parte de los sistemas enzimáticos. —

Estamos lejos de las teorias que prevalecieron desde 1880 hasta cerca de 1910, que atribuian el papel de las secreciones internas a una pretendida capacidad de neutralizar o destruir tóxicos del metabolismo intermedio. — Hoy está demostrado que la función de los órganos endocrinos es elaborar y segregar hormonas reguladoras de procesos del metabolismo general o el de órganos determinados — Basta recordar el papel de la insulina en el metabolismo de los hidratos de carbono o el de las paratiroides sobre el metabolismo de calcio o el de la tiroides en el consumo de oxigeno y la calorigénesis. — En muchos casos, las hormonas regulan procesos quimicos que rigen la morfogénesis, como lo demuestran el papel

(English Translation of the Adjacent Text Submitted in Spanish by Professor B. A. Houssay of Buenos Aires, Argentina.)

Endocrinology is concerned with the study of the action of hormones; these are regulators of important functions of the organism under normal and pathologic conditions. — Hormones are organic substances specifically produced by the glands of internal secretion; once discharged into the circulating fluids (internal medium), they reach all parts of the organism and exert an important influence upon the functions of certain cells and systems, working in small quantities and without contributing by themselves important amounts of substance or energy. —

The hormones regulate important chemical and functional processes of the organism, being probably capable of modifying the course of fundamental enzymatic reactions, there is no proof however that they themselves participate in enzyme systems. —

We are far from the theories which prevailed from 1880 to 1910, which attributed to the internal secretions the rôle of neutralizing and destroying the toxic substances arising in intermediate metabolism. — It has now been proven that the function of endocrine organs is to elaborate and secrete regulators of general metabolic processes and of specific organs. — It suffices to mention the rôle of insulin in the metabolism of carbohydrates, or that of the parathyroids upon calcium metabolism, or that of the thyroid upon the consumption of oxygen and upon heat production — In many cases the hormones regulate

de la hipófisis, la tiroides, el testículo o el ovario sobre el crecimiento y la constitución morfológica — Las acciones hormonales repercuten también intensamente sobre las funciones nerviosas, el comportamiento y el psiquismo; basta recordar la acción que producen las hormonas masculinas o femeninas y la de la castración, la acción de la tiroides o el atiroidismo, etc. —

El papel regulador de las glándulas endocrinas tiene, en muchos casos, una importancia vital. — Así, la falta de las suprarrenales provoca trastornos químicos que llevan a la muerte si no se administran hormonas, sales adecuadas y una dieta apropiada. — Las glándulas endocrinas tienen también influencia sobre ciertos procesos de inmunidad y resistencia del organismo —

Cada glandula de secreción interna tiene una regulación que mantiene su secrecion a un nivel determinado, de acuerdo con las necesidades del organismo. — Así, la hiperglucemia aumenta la secrecion de insulina y la hipoglucemia la disminuye, con lo que la glucemia vuelve al nivel normal y también la secreción de insulina. — Pero aunque muchas glándulas endocrinas intervienen en una función determinada (ej · metabolismo de los hidratos de carbono) hay un equilibrio entre sus secreciones, lo cual asegura la homeostasis del organismo. — Hay entre las glandulas endocrinas acciones reciprocas que las mantienen en equilibrio funcional (ej la relacion hipofisogonadal) —

Por todos estos mecanismos, las glándulas de secreción interna contribuyen poderosamente a asegurar la unidad del organismo, la correlación de sus partes y el equilibrio de sus funciones —

En algunos casos patológicos se rompe o desvía esta regulacion y este equilibrio, ya sea porque un organo endocrino no es capaz de segregar bastante cantidad de hormona para man-

chemical processes which direct morphogenesis as shown by the rôle of the hypophysis, the thyroid, the testis or the ovary upon growth and morphologic structure. — The hormones also exert intense actions upon the function of the nervous system, behaviour and psychologic processes; it suffices to recall the action exerted by the male or female hormones or by castration and the actions of the thyroid or of thyroid deficiency, etc. —

In many instances the regulating rôle of the endocrine glands is of vital importance. Thus adrenal deficiency causes chemical changes conducive to death unless appropriate hormones, salts and diets are administered — The endocrine glands also exert an influence upon certain immunologic processes and upon the resistance of the organism. —

Every endocrine gland possesses a regulating mechanism which maintains its secretion at a certain level in accordance with the requirements of the organism. — Thus hyperglycemia augments the secretion of insulin, while hypoglycemia diminishes it so that both the glycemic levels and the secretion of insulin return to normal — However, although many endocrine glands intervene in a specific function (e g, carbohydrate metabolism) there is an equilibrium between their secretions, which assures homeostasis of the organism — There are between the endocrine glands reciprocal interactions which maintain them in a functional equilibrium, (e g., the hypophyseogonodal interrelation). —

Through all these mechanisms the glands of internal secretion contribute significantly towards the assurance of the unity of the organism, the correlation of its parts and the equilibrium of its function. —

In some pathologic cases this equilibrium is broken or deranged either because one of the organs is unable to secrete a sufficient quantity of hormone to maintain the homeostasis (e.g, hypo-

tener la homeostasis (ej. : hipotiroidismo, diabetes, insuficiencias sexuales, etc.) o bien, en otros casos, porque los órganos endocrinos pierden la capacidad de moderar los aumentos de su secreción para mantener un nivel hormonal normal y entonces se observan síndromes de hiperfunción (ej.: hipertiroidismo, hipercorticalismo adrenal, híperinsulinismo, acromegalia, etc.). — Esto se observa principalmente en casos de adenomas de órganos endocrinos. —

Los órganos endocrinos contribuyen a las reacciones del organismo cuando se producen circunstancias de emergencia. — Tal el caso de la hipersecreción de adrenalina en la hipoglucemia o hipotensión o durante la cólera o el terror o el miedo (Cannon). — El papel de los órganos endocrinos en el síndrome de adaptación general del organismo ante factores vulnerantes físicos o químicos o ante excesivas demandas fisiológicas, ha sido brillantemente demostrado por Selye. — Según sus estudios estas reacciones, que al principio son generalmente favorables, pueden luego por su exceso y repetición, llegar a ser desfavorables y producir estados patologicos, tal como la nefroesclerosis, la hipertensión arterial, lesiones miocárdicas, periarteritis, etc., (Selye). —

En ciertos casos patologicos, se observan secreciones internas que producen enfermedades. — Así, el riñón isquemiado vierte en la sangre renina, la cual en presencia de hipertensinógeno produce hipertensina — Esta última y quizás algún otro mecanismo humoral provoca una hipertensión arterial.

Ciertos desequilibrios hormonales pueden causar tumores benignos de diverso tipo. — Así, los estrogenos en exceso producen adenoma hipofisario, fibroides subperitoneales, metaplasias endometriales, etc , y a la larga favorecen la producción de canceres de la mama o del útero, etc —

thyroidism, diabetes, sexual insufficiencies, etc.) or in other cases, because the endocrine organs lose their ability to moderate rises in their hormone secretion in order to maintain a normal hormone level and then hyperfunctional syndromes arise (e.g., hyperthyroidism, adrenal hypercorticalism, hyperinsulinism, acromegaly, etc.). — This is observed mainly in the case of adenomas of endocrine organs. —

The endocrine organs contribute to the reactions of the organism when an emergency situation arises. — This is the case in the event of adrenaline secretion during hypoglycemia or hypotension, or during rage or terror or fear (Cannon). — The rôle of the endocrine organs in the general-adaptation-syndrome of the organism, when confronted with physical or chemical damaging agents or excessive physiological demands, has been brilliantly demonstrated by Selye. — According to his studies these reactions, which in principle are generally favorable, can become damaging due to excess or frequent repetition; then they result in pathologic conditions such as nephrosclerosis, arterial hypertension, myocardial lesions, periarteritis, etc., (Selye). —

In certain pathologic cases internal secretions can produce diseases. — Thus the ischemic kidney discharges renin into the blood, which in the presence of hypertensinogen produces hypertensin. — The latter, and perhaps also some other humoral mechanism, produces arterial hypertension —

Certain derangements in the hormonal equilibrium may cause benign tumors of various types — Thus, excesses of estrogens produce hypophyseal adenomas, subperitoneal fibroids, endometrial metaplasia, etc., and in the long run they favor the production of mammary and uterine cancers, etc —

Endocrinology is a very young branch of the Biological Sciences — The first facts to be acquired were in

La Endocrinología es una rama muy joven de las Ciencias Biológicas. — Los primeros conocimientos fueron anatómicos; así por ejemplo se distinguieron los caracteres sexuales y las consecuencias de la castración. — Luego la observación clínica mostró la existencia de enfermedades endocrinas, como ser la de Addison, bocio endémico y exoftálmico, mixedema y cretinismo, acromegalia, etc. — Más tarde, la experimentación fisiológica permitió analizar las insuficiencias debidas a la ablación glandular y el papel de los extractos. — En este siglo, se descubrieron las hormonas por obra de químicos orgánicos, en especial desde hace 20 años, se prepararon muchas sintéticamente y se encontraron sustancias artificiales de acción semejante a ellas. —

La Endocrinología se ha desarrollado y sigue creciendo debido a las investigaciones científicas fundamentales desinteresadas. — Pero a la vez es una ciencia de aplicaciones cada vez más grandes en la Medicina y la Zootecnia. — Ha dado lugar a una industria química y farmacéutica poderosa, que por un lado ha ayudado económica y técnicamente a su adelanto, pero que ha estimulado el empleo excesivo de la hormonoterapia. — El prestigio de la Endocrinología le ha valido una reputación llena de errores y fantasías — Por eso son necesarios los libros como éste, que exponen en forma precisa y crítica el estado real de los conocimientos. —

La Endocrinología comprende conocimientos anatómicos, fisiológicos, bioquímicos, genéticos, patológicos, clínicos y zootécnicos — Como ciencia biológica estudia la función de las glándulas endocrinas y el papel de las hormonas en los organismos vivientes. — Como rama de la Medicina procura asegurar la salud, prevenir las enfermedades, diagnosticarlas precozmente para tratar de curarlas o aliviarlas — Desde que las hormonas regulan pro-

the realm of anatomy; thus, for example, the sexual characteristics and the consequences of castration became known. — Subsequently, clinical observation showed the existence of endocrine diseases such as Addison's disease, endemic and exophthalmic goiters, myxedema and cretinism, acromegaly, etc. — Later, physiologic experimentation made it possible to analyze the insufficiencies due to ablation of glands and the rôle of extracts. — During the present century hormones have been discovered as the result of the work of organic chemists; especially during the last 20 years many of the hormones have been prepared synthetically and artificial substances have been found whose actions were similar to those of the hormones. —

Endocrinology has developed and continues to grow due to fundamental, detached scientific investigations. — However, at the same time it is a science with ever increasing medical and zootechnical applications — It has given rise to a powerful chemical and pharmaceutic industry, which in turn helped its economic and technical development, but stimulated the excessive employment of hormone therapy. — The prestige of endocrinology has consequently suffered from the ill-repute of many errors and fantasies. — It is for this reason that books, such as the present one, are necessary to outline in a precise and critical form the real status of our knowledge. —

Endocrinology comprises anatomic, physiologic, biochemical, genetic, pathologic, clinical and zootechnical data — As a biologic science it studies the functions of the endocrine glands and the rôle of the hormones in the living organism. — As a branch of medicine it endeavours to safeguard health, to prevent diseases and to diagnose them at an early stage in order to cure or alleviate them. — Since the hormones regulate fundamental biochemical processes it is evident that every specialist

tener la homeostasis (ej. : hipotiroidismo, diabetes, insuficiencias sexuales, etc.) o bien, en otros casos, porque los órganos endocrinos pierden la capacidad de moderar los aumentos de su secreción para mantener un nivel hormonal normal y entonces se observan síndromes de hiperfunción (ej.: hipertiroidismo, hipercorticalismo adrenal, hiperinsulinismo, acromegalia, etc.). — Esto se observa principalmente en casos de adenomas de órganos endocrinos. —

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estudios originales realizados con hábiles técnicas. — Su erudición excepcional se aprecia en este libro que es una presentación básica y unitaria del problema. — La escasez del espacio le obliga a veces a una exposición algo dogmática y densa en información, per ésta podrá ampliarse recurriendo a las citas bibliograficas que aconseja el autor. —

El libro es un atlas, ademas de un texto, pués se incluyen ilustraciones de todo lo que puede ser fotografiado (histologia, cristales de hormonas, experimentos, radiografias y casos clinicos).

Este libro, a pesar de sus cualidades de excepción, no obliga a un acatamiento dogmatico, pués no expone conocimientos terminados. Su lectura será un punto de partida indispensable para los principiantes y aún para los especialistas; los primeros completarán luego sus conocimientos, cuando sec necesesrio, en el estudio de los materiales clinicos o experimentales y en trabajos especiales más detallados. —

Es indudable que este libro tendrá una importancia histórica, pués es la sintesis más completa publicada hasta hoy de los conocimientos endocrinológicos actuales y los difundirá con eficacia no igualada. Además estimulará los estudios y promoverá las investigaciones que harán adelantar la Endocrinologia. — Como todos los textos no satisfará en cada punto a todos los especialistas y criticos, pero es indudable que este libro tendrá una influencia decisive para difundir los conocimientos exactos y para promover las investigaciones que harán adelantar la Endocrinologia. —

Bernardo A. HOUSSAY

His exceptional erudition can be appreciated in this book which is a basic and unitarian presentation of the problem. — The limitation of space obliges him sometimes to be somewhat dogmatic in his exposition or to condense the information; however, the latter may be expanded by reference to the bibliography recommended by the author. —

In addition to being a text, the book is also an atlas since it contains illustrations of everything that can be photographed (histology, crystals of hormones, experiments, X-rays of clinical cases).

This book, in spite of its exceptional qualities, does not oblige to a dogmatic adherence since it describes an unfinished field of knowledge. Reading of the book will be an indispensable point of departure for beginners as well as for specialists; the former will subsequently complete their knowledge when necessary by the study of clinical and experimental material and of more detailed treatises. —

It is indubitable that this book will possess an historic importance, since it is the most complete synthesis of endocrinologic facts published up to date and it will disseminate these with unequalled efficiency. It will furthermore stimulate studies and promote investigations which will help the progress of endocrinology. — Like all texts it will not satisfy all specialists and critics in every detail; however, it is indubitable that this book will have a decisive influence upon the dissemination of exact data and the promotion of investigations conducive to the progress of endocrinology. —

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cesos bioquimicos fundamentales se comprende que todo especialista en Endocrinologia debe serlo del metabolismo y que inversamente todo especialista en enfermedades de la Nutrición debe conocer la Endocrinologia. — Por ejemplo, la diabetes es una enfermedad del metabolismo por trastorno endocrino (insuficiencia de insulina, etc.). —

Este libro representa una ordenación critica y concisa de lo más importante que se conoce en el inmenso causal de hechos de la Endocrinologia moderna, que es tan vasta que hay especialistas en numerosos problemas parciales y pocos que conozcan todo su campo de estudio. El autor de este libro no ha procurado exponer sólo los hechos acumulados, sino extraer los principios fundamentales que derivan de ellos, recordando que sólo hay Ciencia de lo General y que de tiempo en tiempo son necesarias las grandes sintesis. —

En un mundo tan vasto de conocimientos es imposible que una sola persona domine con igual competencia todos los aspectos de la endocrinologia. — Selye reune para ello condiciones y aptitudes excepcionales y probablemente únicas. Posee la biblioteca endocrinológica más grande del mudno, admirablemente organizada. — Su dominio exceptional de numerosos idiomas le permite comprender el pensamiento propio de diversos paises y culturas y evitar el provincianismo tan frecuente aún en las más grandes naciones — Además, para que el libro sea una exposición objetiva de la Endocrinologia contemporánea, el autor ha hecho revisar cada capitulo por algunos de los más sobresalientes expertos en el tema. — Selye es un brillante expositor y tiene el arte de explicar con claridad y método — Tiene conocimiento personal de la mayor parte de la endocrinologia experimental, en sus aspectos anatómicos y fisiológicos, pues ha contribuido a su adelanto con importantes

in endocrinology must also be one of metabolism and that conversely, every specialist in the diseases of nutrition must know endocrinology. — For example, diabetes is a disease of metabolism due to an endocrine lesion (insulin insufficiency, etc.). —

This book represents a critical and concise, orderly presentation of what is most important in the immense collection of facts of modern endocrinology, a science so vast that there are specialists in numerous branch problems and few who know this entire field of study. The author of this book not only succeeded in describing the accumulated facts but also to crystallize those fundamental principles which are derived from them, thus emphasizing that there is only a science of the general and that from time to time the need for a great synthesis arises. —

In such a vast field of knowledge it is impossible that a single person could dominate all aspects of endocrinology with equal competence. — Selye possesses exceptional and probably unique conditions and abilities for this — He owns the largest endocrinologic library in the world, a collection which is admirably organized — His exceptional command of numerous languages allows him to understand the characteristic thoughts and cultures of diverse countries and to avoid the provincialism so common even in the greatest nations — Furthermore, in order to make the book an objective exposition of contemporary endocrinology, the author has submitted each chapter for revision to some of the most eminent authorities in that particular field. — Selye is a brilliant teacher and knows the art of how to explain things clearly and methodically. — He possesses a personal knowledge of the major part of experimental endocrinology, in its anatomic and physiologic aspects; furthermore, he has contributed important original studies, executed with skilful technique, to the development of the science

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PREFACE TO SECOND EDITION

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In view of the rapid progress made in the field of endocrinology, it has been considered advisable to prepare a second edition as soon as two years after the first. This provided a welcome opportunity to modify certain sections in accordance with suggestions made by many colleagues throughout the world. At the same time, the most important recent discoveries published during the last two years have been included, new important key references have been added and several of the pictures have been replaced by more adequate illustrations. The section "Commercial Hormone Preparations" had to be completely rewritten. In order to avoid any extensive changes in the complex subject index, this was accomplished without change in pagination.

Truly fundamental changes were not necessary and hence, we cannot recommend the book to those who already own the first edition, unless they are particularly anxious to be kept entirely up to date.

HANS SELYE

Université de Montréal
1949

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INTRODUCTION

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The history of medicine shows that whenever a great deal of progress is made in one particular field, individuals (specialists) and books (textbooks and encyclopedic surveys) emerge, with the aim of correlating all the data pertaining to this new subject. These individuals and books depend upon each other. Only a highly specialized physician can write a book concerning an entire branch of science, but, conversely, such books are essential in acquiring the specialist's knowledge. Therefore the work of several generations is usually necessary before a body of data is gradually molded into a recognized separate branch of science.

During the period of its development it is of the greatest importance to delimit the new science from other fields of knowledge, so that it comprises all those facts which lend themselves particularly well for conjoint study by the same individual. The inability of the human mind to master more than a limited field of knowledge is the only justification for the development of specialties and specialists

A survey of the medical sciences clearly indicates how time-taking it is to draw precise and logical borderlines for a specialty. Anatomy and, to a somewhat lesser extent, its younger sister science histology, are perhaps the best examples of old and well-established specialties, whose contents are clearly outlined by our traditions, based on generations of experience. As a result of this, the anatomists and anatomy books of all countries agree surprisingly well on the data which are pertinent to this science, as well as on the classification and order of presentation of relevant material for didactic purposes. The pertinent facts are either arranged according to organ systems or according to their topographic relations. We do not even think of any other possible classification, although a priori, presentation of organs and tissues according to similarities in their chemical composition (water, fat, protein, carbohydrate content, etc.); embryologic development (ectodermal, mesodermal, entodermal organs) and many other points of view might appear to be equally satisfactory. The outlines of histology or pathologic anatomy, representing somewhat younger sciences, are slightly less clearly defined by tradition than those of anatomy. In all these relatively old morphologic sciences, however, the delimitation from other branches of medicine is so generally accepted that most contemporary schools closely agree on the type of routine training they should expect their morphologists to possess and to transmit to their students.

Such standardization of outlines and contents becomes increasingly more difficult with the sciences which are still in the process of active growth. Internal medicine, pediatrics, gynecology and obstetrics for instance, are fairly well standardized specialties, while dietetics, biochemistry, public health and social medicine still expand so rapidly that the specialists and specialized books con-

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cerned with these subjects vary greatly in their interpretation of what is relevant to these disciplines.

Endocrinology is one of the youngest and most rapidly expanding fields of medicine; hence, there are comparatively few books which attempt to survey the entire subject and those which exist, exhibit marked differences in their conception of this field. This is partly the cause and partly the result of the fact that in our time there still are only very few professional endocrinologists. There are physicians specializing more or less exclusively in the treatment of diabetes, thyroid diseases, gynecologic endocrinology or even in all of clinical endocrinology, but their interest in the anatomy, embryology or pathologic anatomy of the endocrines is usually limited. There are excellent chemists who have done a great deal to further our understanding of the chemical structure of hormones and to supply us with the many synthetic hormone preparations now available. However, most of them consider the morphologic and clinical aspects of endocrinology entirely outside their field. Zoölogists, physiologists, pharmacologists or biochemists may take up one or the other endocrine research problem; and perhaps even teach an endocrinology course at a university, but in the absence of comprehensive standard books and post-graduate courses, they find it almost impossible to acquire the training necessary to master the whole field.

During the sixteen years in which I have taught endocrinology, first at McGill University, and more recently at the Université de Montréal, I have learned that there is a great demand for "professional" endocrinologists to supplant the "amateurs" of this science in universities, hospitals, the pharmaceutic industry, etc Specialists with a rounded general training in all problems pertaining to the hormones would be singularly well-prepared for the teaching and clinical practice of endocrinology, as well as for investigative work in any of its branches. Our teaching institutions would not think of acknowledging the competence of a surgeon, a radiologist or a dermatologist who has not had the benefit of special post-graduate training in his field For general medicine, chemistry, physics, etc., we even supply standardized undergraduate courses. However, anyone may call himself an endocrinologist, because no school has organized a systematic post-graduate training schedule for those who wish to become specialists in this subject.

The present textbook is one of three tasks undertaken by our Institute in an attempt to delimit and systematize the field of endocrinology and to help those who wish to specialize in this science.

(1) We have compiled a library containing an almost complete set of all original articles and books dealing with the hormones. This collection which now comprises about 250,000 entries (reprints, books, microfilms, photostats, abstract cards, etc.) serves as a basis for the publication of the "ENCYCLOPEDIA OF ENDOCRINOLOGY," which, it is hoped, will ultimately act as a critical survey and a complete guide to the entire endocrinologic literature. Up to now, six volumes of this treatise have appeared in print, and the classification of the literature as well as a large part of the remaining manuscript have been completed for future publication. This treatise is designed mainly as a research tool for the specialist and original investigator.

(2) The present "TEXTBOOK OF ENDOCRINOLOGY" represents a miniature of the Encyclopedia, in the form of a concise, and we hope, balanced summary of the most important and best-established facts concerning all branches of our science. It is designed primarily for the medical student and physician,

but also for specialists in endocrinology or in a more general subject (zoölogy, biochemistry, physiology, pathology, etc.) in which endocrinology represents a cognate science.

(3) We have planned a SYSTEMATIC POST-GRADUATE COURSE in endocrinology, which is now given at this Institute. The object of this course — which leads to the Ph.D. degree — is to give both theoretical and practical training in the entire field of endocrinology. In addition to supervised research and post-graduate courses the candidates are required to take a "rotating internship" in the five sections of the Institute (Experimental Surgery, Pharmacology, Biochemistry and Nutrition, General Physiology and Experimental Morphology). Thus they are given an opportunity to familiarize themselves, at least to some extent, with the interest and technics of the investigators in charge of these divisions. After surveying comparable courses in other Universities, it appeared to us that although many centers give excellent post-graduate tuition in certain branches of endocrinology, few, if any, have attempted to offer a systematic post-graduate course covering the entire subject. Hence, we hope that experimentation with such a course in our school may help other centers, if not to emulate our methods, at least to avoid our errors.

But let us return to this textbook. Some readers will perhaps deplore the paucity of references. It is true that only a few outstanding monographs and reviews are quoted at the end of each chapter, but these act as a guide to a large number of pertinent original articles. It is our experience that readers of textbooks rarely consult original articles cited in support of individual statements in the text If references are given to prove specific points, it is indispensable to quote the entire pertinent literature as we attempted to do in the Encyclopedia of Endocrinology. Indeed, if only selected references are quoted — as is generally the case in textbooks — they tend to mislead the reader into believing there are no other, perhaps contradictory, data in the relevant literature. Such references may help to shift the responsibility from the writer of the textbook to the author of the original article, but they merely mislead those who do not have the time to make a detailed study of each question.

In perusing textbooks dealing with various branches of medicine, it is striking that the number of references quoted is so often inversely proportional to the degree of certainty with which the author feels competent to discuss the matter. Almost no references are given in textbooks of anatomy or histology, and even elementary treatises of internal medicine rarely cite much of the original literature on which the discussions are based. It is unnecessary to quote the authorities who described the branches of the internal carotid artery, the chromaffinity of adrenal medulla cells, the branching of heart muscle fibers, or the classic symptoms and signs of lobar pneumonia Everybody agrees on these points and the author of the textbook is quite prepared to accept the responsibility for them. On the other hand, it is convenient to quote others when we discuss the biogenesis of the steroid hormones, or the mechanism of parathyroid-hormone action since pertinent theories are likely to be incorrect.

I am quite prepared to state at the onset that the views expressed in this book are mine I arrived at them, partly by personal observation and partly through the evaluation of literature compiled for the *Encyclopedia of Endocrinology* This book will undoubtedly prove to contain errors of omission and commission Nothing would be gained, however, by shifting the responsibility for any inaccuracies upon a limited number of references, which would have to be selected on an arbitrary, and hence subjective basis in any case By

the same token, I have carefully avoided quoting any of my own original publications. Had I done so, the reader could have gained the impression that it is only for the statements made in these that I am prepared to vouch. My own investigations added but little to the subject matter reviewed in this textbook, hence as an original investigator, I cannot be credited or blamed for more than a negligible portion of it. However, in addition to his original observations an author is also responsible for the evaluation of his data and their correlation with other reports in the literature. The interpretation of data and theories is naturally more subject to error than the mere report of observations. Yet the correlation of facts is an integral part in the structure of any science, and in this latter sense, the author of a textbook should also be prepared to be quoted for statements which reflect his judgment. I have undoubtedly made many errors, but I think that the readers of a textbook are more interested in the author's personal views expressed after weighing the relevant data to the best of his ability in the light of his experience, than in his legalistic skill to avoid possible blame by non-committal phrases and quotations.

As a result of these principles, the book suffers from many shortcomings. Firstly it is perhaps too dogmatic. Yet, whenever the evidence failed to convince me, I tried not to give the impression of unwarranted certainty, formulating the definiteness of my conclusions in proportion to the evidence at hand.

Secondly the book can hardly be called amusing. My only excuse for the heaviness of my style, is that my first concern was the concise expression of all the best-established facts. This left no space for colorful descriptions or stimulating speculations, if the book was not to become too bulky. However, I have tried to mitigate the austerity of the text by many illustrations

If the structure of the book will prove to be a logical outline of the natural borders of Endocrinology and if the readers will be able to find concise and correct statements concerning the most important pertinent facts known to us at present, it will have fulfilled its purpose as a standard text. I shall have to rely upon the teachers of this subject to add, through colorful and stimulating lectures, the enthusiasm which this interesting field of medicine deserves I shall be entirely satisfied if in turn, the teachers find that by having described the factual matter in the book, they can devote more time during their lectures to digressions from the drab routine

Finally I should like to ask my readers to *make suggestions concerning possible improvements in this book.* I found it very difficult and timetaking to write the entire volume myself. I undertook to do it, because textbooks in which various chapters are written by different authors, usually lack unity and balance. To some extent, however, a good textbook should be a cooperative enterprise in which readers, and especially experienced teachers and investigators, collaborate with the author in his effort to adjust the volume to current requirements in subsequent editions. In this respect I must count on the help of my colleagues, but conversely, I would like them to feel assured that no effort will be spared to make and keep the book a true spokesman of contemporary endocrinology

Hans SELYE

Université de Montréal
1947

ACKNOWLEDGMENTS

During the rather arduous task of compiling material for this book it was one of my most pleasant experiences to note how strong the spirit of coöperation has remained among the scientists throughout this war-torn world. I have called upon many of my colleagues for advice and illustrative material not readily available to me and it was most gratifying to note that scientists of so many lands several of whom I have never met, invariably responded in the most coöperative manner and spared no effort to furnish me with the information or material required. This exhibition of international fraternity among scientists was so heart-warming that I should like to enumerate the names of those who gave me aid, arranging them according to their countries of origin

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Many of these colleagues helped me by criticizing and proof-reading sections of the manuscript while others supplied illustrative material Space would not permit me to describe the nature of the participation of each individual in more detail here but the names of those who furnished me photographs or material for illustrations is specifically listed under the figure which they helped to provide

I could not write this acknowledgement however without specifically emphasizing my most profound indebtedness to Professor *B A Houssay* of Buenos Aires for writing the foreword to Doctor *E Perry McCullagh* of the Cleveland Clinic for having contributed the largest number of photographs concerning clinical endocrinology, to the late Doctor *E Kepler* of the Mayo Clinic for criticizing and improving the chapter concerning the adrenals to Mr *K Nielsen* for having prepared all photographs illustrating material provided by our Institute to Mr *Alex Thersen* for the excellent printing of this book (a task which under the present post-war conditions was not an easy one) and last but not least to my colleague Miss *Helen Stone* of this Institute who proof-read and edited the entire manuscript after each chapter had been submitted to the scrutiny of a specialized investigator

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	Grauer, Robert C	Department of Research in Endocrinology and Metabolism Allegheny General Hospital,	N S Pittsburgh Pa
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	von Haam Emmerich	Department of Pathology The Ohio State University	Columbus Ohio
	Henriksen Erle	Department of Gynecology University of Southern California	Los Angeles Cal
	Karsner H T	Army Institute of Pathology, Army Medical Museum	Washington D C
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GENERAL ENDOCRINOLOGY

•

DEFINITION AND SCOPE OF ENDOCRINOLOGY

DEFINITION OF ENDOCRINES AND HORMONES

It is rather difficult to define the natural confines of endocrinology. According to classic MORPHOLOGIC concepts, endocrinology is a science concerned merely with the glands of internal secretion, on a FUNCTIONAL basis, however, it deals with all hormonal substances even those produced by organs other than the exclusively endocrine glands. These definitions of the field are obviously dependent in turn upon a clear understanding of what we mean by endocrine organs and hormones respectively.

The Endocrine Organs. — On morphologic grounds, the hormone (for definition, see below) producing organs may be classified into three groups, namely:

(1) PURELY ENDOCRINE GLANDS, whose only function is to produce hormones. Among these, we distinguish the "*storage type*" (as exemplified by the thyroid), in which the endocrine cells are arranged in the form of small follicles The lining cells can secrete directly into the blood stream or store their secretion in the follicular cavity. At times of high hormone requirement, the stored material is reabsorbed by the lining cells and transferred into the blood

The "*solid type*" of endocrine gland (as exemplified by the parathyroids) contains no storage spaces. The parenchyme consists of massive cords or nests of epithelial cells, whose secretory products are discharged directly into the blood stream. Some degree of storage is possible even in these glands, but here the hormone accumulation is exclusively intracellular.

(2) ENDO-EXOCRINE GLANDS, which secrete hormones into the blood stream, but, at the same time, also produce an exocrine secretion eliminated through a duct system. This group may be further subdivided into two sub-groups.

In the "*mixed endo-exocrine glands*" (as exemplified by the pancreas) parts of the organ are purely exocrine (the acinar tissue), while other parts are exclusively endocrine (the Langerhans islet tissue); the latter component, in this instance is a "solid type" of an endocrine gland Anatomically, the two portions are intermixed.

On the other hand, the "*simple endo-exocrine glands*" (as exemplified by the liver) contain only one type of parenchymatous cell, which simultaneously, produces both an exocrine secretion eliminated through ducts (bile) and a hormone-like substance secreted directly into the blood stream (the anti-pernicious-anemia factor).

(3) NON-GLANDULAR ENDOCRINE ORGANS such as the adrenergic and cholinergic nerves, produce hormone-like substances (acetylcholine and sympathin) without subserving any exocrine function Some hormone-like substances (e g., histamine) can probably be produced in a similar manner by several non-glandular organs.

According to classic concepts, only the purely endocrine cells are regarded as parts of the true endocrine system. The endocrine portions of mixed endo-exocrine glands (e.g., Langerhans islets) are of course always included since they subserve no function other than hormone production

The Hormones. — On a purely *functional basis*, endocrinology must include all hormone-producing organs, irrespective of their morphologic structure. The only justification for the purely *morphologic* type of classification is that its outlines are more clear-cut, because it is simpler to recognize purely endocrine structures on a histologic basis than it is to delimit hormones from other active metabolites on functional criteria.

For any functional classification, it is essential to define what we understand by a HORMONE. This term (from the Greek "hormao" = I stir up or stimulate) was introduced by *Bayliss and Starling* (1902), who defined a hormone as "any substance normally produced in the cell of some part of the body and carried by the blood stream to distant parts which it affects for the good of the organism as a whole." *Sharpey-Schafer* (1924) introduced the term "AUTOCOID" meaning "a specific organic substance formed by the cells of one organ and passed from them into circulating fluids to produce effects upon other organs, similar to those produced by drugs." He wanted to retain the term "hormone" as a generic designation to include pharmacologically active metabolites produced by any organ. In this sense, CO_2, histamine, acetylcholine, sympathin, etc., would also be hormones, but not autocoids. However, this distinction is somewhat artificial, and the term autocoid has fallen into disuse.

More recently a number of highly active regulators of cellular differentiation and activity (embryonic organizer, wound hormones, etc.) have been regarded by some investigators as "INTRACELLULAR HORMONES." These differ from generally recognized hormones mainly in that they act locally in or around the cells in which they are formed.

The number and cumbersome formulation of the above definitions show how difficult it is to delimit these concepts. In some sciences (e.g., mathematics) definitions are unchangeable laws, which make a concept what it is. In biology, however, definitions are given merely as concise descriptions of phenomena as they are known at the time. They are formulated with the view of modifying them as soon as further observations necessitate it. With this in view, it may suffice, at this time, to define hormones and endocrines as follows:

HORMONES ARE PHYSIOLOGIC, ORGANIC COMPOUNDS PRODUCED BY CERTAIN CELLS FOR THE SOLE PURPOSE OF DIRECTING THE ACTIVITIES OF DISTANT PARTS OF THE SAME ORGANISM.

ENDOCRINE ORGANS ARE ALL THOSE WHICH PRODUCE HORMONES.

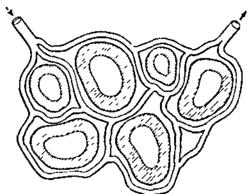
These definitions are formulated to include all the most generally accepted characteristics of hormones and endocrine organs. The following criteria are regarded as essential:

Hormones are *physiologic* compounds, since it is not customary to include among them active substances (e.g., antibodies, toxic metabolites released by injured cells) which are not necessarily produced under physiologic circumstances.

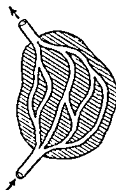
Only organic compounds are classed among the hormones, since minerals released by cells are not included in this concept, even though they may be discharged for the sole purpose of directing the activities of distant parts.

Hormones are produced for the *sole purpose of directing, regulating and coordinating the activities* of the organism. Substances which direct only by supplying nutritive material and those which are merely catabolites of cells with incidental regulatory functions are not hormones. In the sense of Bayliss and Starling's definition, a nutrient such as glucose produced by hepatic cells would be a hormone, since it is "carried

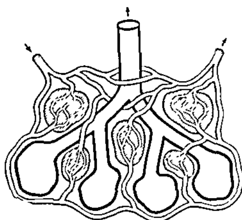
Morphologic classification of the endocrine glands



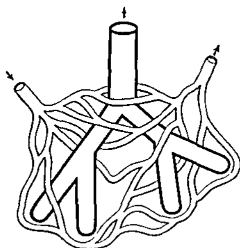
1 STORAGE TYPE OF ENDOCRINE GLAND as exemplified by the thyroid



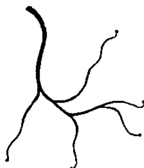
2 SOLID TYPE OF ENDOCRINE GLAND as exemplified by the parathyroids



3 MIXED ENDO-EXOCRINE GLAND as exemplified by the pancreas



4. SIMPLE EXO-ENDOCRINE GLAND as exemplified by the liver.



5 NON-GLANDULAR ENDOCRINE ORGAN as exemplified by adrenergic nerve endings

with consequent hormone overdosage, or destruction of incretory organs with the resulting hormone deficiency syndromes, are instructive, simple experiments of nature, which have taught us much about the endocrines. But these are rare diseases in comparison with the hormonal derangements resulting from maladaptation to stress.

The main, fatal syndromes of internal medicine (various cardiovascular, renal, "rheumatic" and old age diseases) may belong to this latter group; they are probably by-products of faulty hormonal adaptive reactions to a variety of non-hormonal pathogenic agents. The apparent cause of illness is often an *infection*, an *intoxication*, nervous exhaustion or merely old age, but, actually, a break-down of the hormonal adaptation-mechanism appears to be the most common ultimate cause of death in man.

THE ORGANIZATION OF CONTEMPORARY ENDOCRINOLOGY

In order to obtain a clear view of the scope of contemporary endocrinology, it is also useful to survey the place it takes in our society.

Research and advanced teaching in endocrinology necessitate a rather complex organization of men, laboratories, hospitals, libraries, etc., hence, throughout the world, the study of this subject is still largely restricted to UNIVERSITIES We need not dwell upon the organization of post-graduate training and university research in endocrinology since this has been discussed in the Introduction.

The participation of PRIVATE INSTITUTIONS (private hospitals not attached to Universities, industrial laboratories) in the development of endocrinology is comparatively limited

A number of SCIENTIFIC SOCIETIES have been formed, in order to promote research and teaching in the field of endocrinology. Among these are the following :

American Association for the Study of Goiter (U S A)

American Diabetes Association (U S A).

Association for The Study of Internal Secretions (U S A).

British Diabetes Association (Great Britain).

Dansk Endokrinologisk Selskab (Denmark).

Dutch Society for Endocrinology (Holland).

Endokrinologföreningen [Svenska Lakaresallskapets Sektion for Endokrinologi] (Sweden).

Endocrinological Society (England).

Finnish Society for Endocrinology (Finland).

Laurentian Hormone Conference (Canada).

Nippon Naibunpi Gakkai (Japan).

Norwegian Society for Endocrinology (Norway).

Pan-American Endocrinological Congress (South America).

Russian Endocrinological Society (USSR).

Sociedad Argentina de Endocrinologia y Nutricion (Argentina).

Sociedad Mexicana de Nutricion y Endocrinologia (Mexico).

Société Canadienne d'Endocrinologie (Canada).

Société Française d Endocrinologie (France).

Many of these have frequent meetings, at which endocrinologic papers are presented, but in most instances, the conventions are held annually or at even longer intervals. Thus the *Association for the Study of Internal Secretions* meets annually, if possible in the city in which the American Medical Association convenes at the same time. Usually, several hundred endocrinologists (mostly from North America) attend; the Meeting being open to all members of the Society, as well as to invited guests. As a rule papers are limited to 10 minutes, followed by a brief discussion. The convention lasts two days

The *Laurentian Hormone Conference* is sponsored by the American Association for the Advancement of Science (A.A.A.S.) and takes place annually in the United States or one of the Laurentian resorts of Canada. Attendance is by invitation, usually limited to about 100 members The meetings are purposely organized in a rather leisurely manner, in order to permit ample time for each paper, as well as the subsequent discussion. The

by the blood stream" and "affects distant parts for the good of the organism as a whole." Sharpey-Schafer's concept of an autocoid hinges upon the, very difficult, definition of what we understand by "drugs." His inclusion of CO_2 among the hormones is likewise contrary to common usage.

We consider it essential that hormones are produced to direct the activities of *distant parts*. It is inadvisable to regard "intracellular hormones" as endocrine substances, since any cell produces a large number of chemical agents which affect the same or adjacent cells. Their inclusion among hormones would deprive this concept of all significance. Such compounds are manifestly not "endocrine" (endon = within; crino = to separate, to secrete), since they are not secreted into internal body fluids, but act locally at the site of their formation

Finally, it is essential to emphasize that hormones affect distant parts of the *same organism* in order to distinguish them from such regulators of cellular activity as animal poisons, or the odoriferous substances produced to repel or attract other animals, etc

If we accept this definition of hormones, the only logical formulation of the concept of endocrine organs is the simple one given above. It is in agreement with common usage, since we speak of the endocrine activity of the liver, kidney, etc., although these glands are not exclusively hormone-producing.

If, in this book, we place special emphasis upon the exclusively endocrine glands and their secretions (more correctly, but less customarily designated as "incretions"), we do so only because these are better known than the hormones of other tissues. It is agreed, however, that in future editions, the scope of this textbook may have to be expanded

DELIMITATION OF ENDOCRINOLOGY

If we accept the view expressed in the introduction that it is logical and natural, "to delimit a new science from other fields of knowledge, so that it comprises all those facts which lend themselves particularly well for conjoint study by the same individual," then endocrinology must embrace all matters pertaining to the hormones That means the normal and experimental morphology of the endocrine glands, the pharmacology and chemistry of the hormones, as well as the many clinical problems raised by the diseases of the endocrines In view of the many correlations between the morphology, chemistry, physiology and pathology of the endocrines, a conjoint study of this vast subject matter by the same individual is sufficiently rewarding to justify this broad formulation of the field. It is impossible, however, to give equal attention to hormones and hormone-like substances produced by organs other than the purely endocrine glands, especially at the present time, when our knowledge concerning these outer areas of our subject is still so limited. As stated in the introduction, it is merely *for this reason that our book places its* chief emphasis upon the purely endocrine glands.

Those, however, who are about to decide whether they should select endocrinology as their main subject, should think of the broader scope of this science and the trend which its development and applications are taking. The following considerations appear to be of significance in this connection.

For the species, the most important rôle of the hormones is reproduction, but for the individual, it is differentiation and adaptation It becomes increasingly more obvious, furthermore that the principal medical application of endocrinology is not the treatment of the primary, but of the secondary diseases of the endocrines. — Tumors *and hyperplasias of endocrine glands*

Bulletins et mémoires, section d'endocrinologie de la société roumaine de Neurologie, Psychiâtrie, Psychologie et Endocrinologie (Roumania).

Endocrinologie, gynécologie, si obstetrica (Roumania).

Endocrine Round Table (U S A).

Endocrine Survey (Continuing the International Digest of Organotherapy) (U S A).

Endocrinologia e pathologia costituzionale (Italy).

Endocrinologia (Italy).

Endocrinology (U S A).

Endokrinologie (Germany).

Folia endocrinologica (Italy).

Folia endocrinologica japonica (Japan)

Hormones (England).

Japanese Journal of Endocrinology (Japan)

Journal of Clinical Endocrinology (U S A)

Journal of Endocrinology (England).

Ormoni (Italy).

Ormonologia: biologia, patologia clinica (Italy).

Reviews in Endocrinology (U S A).

Revista sud-americana de endocrinologia, immunologia y quimioterapia (Argentina)

Revue française d endocrinologie (France).

Transactions of the American Association for the Study of Goiter (U S A)

Vitamine und Hormone (Germany)

Vitamines and Hormones (U S A)

Since endocrinology touches upon almost every other field of medicine and physiology, numerous pertinent publications appear in *journals not primarily devoted to the endocrines*. Among these, we mention the following as important sources of current endocrinologic literature :

Acta Anatomica (Switzerland).

American Journal of Obstetrics and Gynecology (U.S.A.).

American Journal of Physiology (U. S A.).

Canadian Medical Association Journal (Canada).

Comptes rendus de la Société de biologie de Paris (France).

Journal of the American Medical Association (U.S A.).

Journal of Physiology (England).

Lancet (England).

Presse Médicale (France).

Proceedings of the Society for Experimental Biology and Medicine (U. S A.).

Revista Argentina de Biologia (Argentina).

Revista Brasileira de Biologia (Brazil).

Revue canadienne de Biologie (Canada).

Surgery, Gynecology and Obstetrics (U.S.A.).

In compiling literature concerning an endocrine problem, the following *indices and abstract journals* prove of considerable value :

Annual Review of Biochemistry (U.S.A.).

Annual Review of Physiology (U. S.A.).

Biological Abstracts (U.S.A.).

Chemical Abstracts (U.S.A.).

Excerpta Medica (Holland).

Index Catalogue of the Library of the Surgeon General's Office (U.S A.).

Physiological Abstracts (England).

Quarterly Cumulative Index Medicus (U.S.A.).

Among the *encyclopedic treatises and handbooks* devoted to endocrinology, the following are noteworthy :

Die Bedeutung der inneren Sekretion für die Frauenheilkunde, von W. Berblinger, C. Clauberg und E. J. Kraus, in Handbuch der Gynäkologie, Dr. W. Stoeckel, Verlag von J. F. Bergmann, Munchen (1936).

Encyclopedia of Endocrinology — by Hans Selye, Richardson, Bond and Wright, Publ., Montreal (1943-1946).

Endocrinology and Metabolism — by Garrison Barker, Appleton Publ. (1922).

Glandes Endocrines, in : Encyclopédie Médico-Chirurgicale — Fondateurs, A. Laffont and F. Durieux, 18, rue Séguier, Paris (6).

Endocrine Medicine — William Engelbach, Springfield, Ill , Baltimore, Md., Charles C. Thomas, Publ (1932).

Handbuch der inneren Sekretion — [illegible] 1933).

convention lasts one week during which time there is a good deal of opportunity for personal contact and exchange of ideas, even outside of formal meetings.

The Pan-American Endocrinological Congress convenes every three years, in one of the South American University Centers. It lasts several days and in addition to short papers (10 to 15 minute papers), some more extensive surveys are presented by invitation. Although most participants (usually several hundred) are South American, many North American endocrinologists attend

In addition to the meetings of endocrinological societies, MANY PERTINENT PAPERS ARE PRESENTED AT THE CONVENTIONS OF SCIENTIFIC ORGANIZATIONS WITH A MORE GENERAL SUBJECT MATTER. Most important among these is the *International Physiological Congress*, which represents the largest group concerned with experimental medicine and physiology. It meets once every three years, usually in Europe or America.

The *Federation of American Societies for Experimental Biology* ("Federated Societies"), represents an association of six learned societies of the United States of America (The American Physiological Society, the American Society of Biological Chemists, the American Society for Pharmacology and Experimental Therapeutics, the American Society for Experimental Pathology, the American Institute of Nutrition and the American Association of Immunologists). It features many papers of endocrinologic interest at the annual convention This group probably has the greatest attendance and presents the largest number of papers (several hundred) among all national societies interested in experimental medicine and physiology Most of the papers are brief (10 minutes), but a few longer symposia are likewise presented. The Federation convenes once annually in various cities of the U.S A.

The *Josiah Macy Jr. Foundation* organizes smaller meetings (attendance of 20 to 30), usually in New York City, at which papers are presented by invitation. Many of the subjects discussed are of endocrinologic interest.

The *American Society for Clinical Investigation* meets once a year (usually in Atlantic City). Attendance is limited to the members and some invited guests. A considerable number of the papers are of clinical endocrinologic interest.

It is well for the young endocrinologist to know about societies and conventions of this type, since they offer opportunities to hear scientific discussions in which specialists from various centers participate At these meetings the student may discuss problems of technic, graduate study, possibilities of inter-laboratory collaboration on endocrine problems, opportunities to obtain laboratory space in institutions at which his work could best be performed, etc *It is important to realize that the meetings* (and the published proceedings) of the scientific societies play a very important rôle in the development of any science, and this is particularly true of a rapidly growing young subject such as endocrinology

The ENDOCRINOLOGIC LITERATURE is so voluminous and grows so rapidly that its publication and classification present many difficult problems of organization

The following is a list of *publications more or less exclusively devoted to endocrinology* Although some of them have temporarily, or even permanently ceased publication, it is important to know about them, since they contain many important papers on hormones

Acta Endocrinologica (Canada)
Acta Endocrinologica (Denmark)
Acta Endocrinologica (Roumania)
Acta Endocrinologica et Gynaecologica (Portugal)
Annales d'endocrinologie (France).
Archivos de la Clinica e del Instituto de Endocrinologica (Uruguay)

Bulletins et mémoirrs, section d'endocrinologie de la société roumaine de Neurologie, Psychiâtrie, Psychologie et Endocrinologie (Roumania).

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Excerpta Medica (Holland).

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Physiological Abstracts (England).

Quarterly Cumulative Index Medicus (U S.A.)

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Glandes Endocrines, in Encyclopedie Médico-Chirurgicale — Fondateurs, A Laffont and F Durieux, 18, rue Séguier, Paris (6).

Endocrine Medicine — William Engelbach, Springfield, Ill., Baltimore, Md , Charles C. Thomas, *Publ* (1932).

Handbuch der inneren Sekretion — *Eine umfassende Darstellung der* Anatomie, Physiologie und Pathologie der *endokrinen Drusen*, ed by Max Hirsch, Curt Kabitzsch Publ., Leipzig (1932-1933)

Metabolism, Endocrine Glands, *in* Nelson New Loose-Leaf Medicine, Thomas Nelson & Sons, Publ. (1941).

Sex and Internal Secretions, a Survey of Recent Research, ed. by Edgar Allen, Charles H. Danforth and Edward A. Doisy, *William & Wilkins* Company, Publ., Baltimore 1st Ed. (1932); Repr. (1934); 2nd Ed. (1939); Repr. (1944).

The *total volume of the endocrinologic literature* is difficult to estimate. The endocrinologic library of this Institute, which, though still incomplete, is the most extensive collection of this kind, contains over a quarter of a million references. Additional publications appear at the rate of approximately 5,000 per annum, hence it is evident that the compilation of publications concerned with a certain problem of *hormone research represents one of the* most difficult tasks met by the contemporary endocrinologist. Once the investigator has succeeded in selecting the references which will be of particular use to him, the Library of the Surgeon General's Office, U.S. Army (Washington, D C.), is willing to supply microfilms to those who have no library facilities at their disposal. The references can be compiled with some degree of efficiency, using the indices, abstract journals and encyclopedias mentioned above. It is difficult to discuss this problem, however, without calling attention to the fact that the compilation of scientific bibliographies needs a great deal of training and a large body of specialized personnel, if it is to be conducted in a systematic manner. Since the necessary books and library staffs are not at the disposal of most endocrinologists, a centralized, international organization of this work would be most desirable. It would certainly be no more expensive than the duplication of amateurish effort which is now in progress throughout the world in so many research centers, dealing with hormone research Essentially, the same could be said about the classification and supply of medical literature in any other field.

The progress of endocrinology has been greatly advanced by SCIENTIFIC FOUNDATIONS, who subsidize pertinent *research work by grants-in-aid.* Although these foundations do not limit their efforts to endocrinology, the following may be mentioned as contributing considerable sums for research on hormones :

1. Commonwealth Fund (U.S.A.).
2. John and Mary Markle Foundation (U.S.A.).
3. Josiah Macy Jr. Foundation (U. S.A.).
4. National Public Health Service (U.S.A.).
5. Rockefeller Foundation (U.S.A.).
6. Sugar Research Foundation Inc., (U S.A.) — *Mainly in connection* with carbohydrate metabolism.

In addition to grants given to institutions for specific research programs, individual *bursaries, fellowships and scholarships* are available for young investigators who wish to specialize in research subjects The following are enumerated as likely sources of support for promising young endocrinologists who cannot complete their training at their own expense :

Rockefeller Foundation Travelling Fellowships.

American National Research Council Fellowships (usually tenable in the U S.A.).

Canadian National Research Council Fellowships (usually tenable in Canada).

Banting Fellowships (usually tenable in Canada)

Beit Fellowships (usually tenable in England).

1851 Fellowships (usually tenable in England).

Royal Society Fellowships (usually tenable in England)

Rhodes Scholarships (usually tenable at Oxford, England).

Life Insurance Medical Research Fund Fellowships (tenable in the U.S A. or Canada).

The PHARMACEUTIC INDUSTRY is taking an ever increasing interest in the manufacture of hormones: many important discoveries concerning, for instance, the isolation, synthesis and bioassay of hormones are due to work performed or subsidized by the major pharmaceutic companies. Among these we may mention the following companies who play a particularly great rôle in supplying the world market with new hormone products :

Abbott Laboratories, Middlesex, England; Montreal, Canada; Chicago, U S.A.

Armour Company, Chicago, Ill., U S.A., London, England.

Ayerst, McKenna & Harrison Ltd., New York, N.Y

British Drug Houses, London England.

Burroughs Wellcome and Co. (U S. A.) Inc., London, England, New York, N.Y., U.S.A.

Byla Company, Paris, France.

Ciba Pharmaceutical Products, Inc., Summit, N.J., U.S.A.

Eli Lilly and Company, Indianapolis, Indiana, U.S.A.

Harrower Laboratory, Inc., Glendale, Cal., U.S.A.

Parke, Davis and Company, Detroit, Mich., U.S A.

Reed and Carnrick, Jersey City, N.J., U.S.A.

Gedeon Richter Ltd., London, England.

Rhone Poulenc, Paris, France.

Roche Organon Inc., Roche Park, Nutley, N.J., U.S.A.

Schering Corporation, Bloomfield, New Jersey, U.S A.

Serotherapeutic Institute of Milan, Italy.

E. R. Squibb, New York, N.Y., U.S.A.

Upjohn Company, Kalamazoo, Mich., U.S.A.

Winthrop Chemical Co., New York, N Y., U S A.

This list is of course very incomplete, and perhaps somewhat arbitrarily selected, since hundreds of pharmaceutic companies produce hormone preparations. It is only intended to familiarize the reader with the names of a few major manufacturers of endocrine products

MECHANISMS OF HORMONE ACTIONS

PREREQUISITES OF HORMONE ACTIONS

The so-called "target organs" or "end organs" do not necessarily react to hormones under all conditions. This is understandable if we consider the mechanisms through which endocrine products exert their actions. From this point of view, we may distinguish three types of hormones :

(1) DIRECTLY ACTING HORMONES. — These are hormones which act upon their targets directly and not through the intermediary of other organs. In general, such hormones affect the receptive cells, even in vitro, since the immediate response they elicit is independent of the rest of the body. The action of adrenaline upon the blood vessels is an example of such a direct hormone action. It occurs even if adrenaline is directly applied to isolated blood vessels

(2) INDIRECTLY ACTING HORMONES. — In themselves, these do not affect the target organ at all. They act upon another organ (usually another endocrine gland) and induce it to produce a hormone which influences the target organ directly. For example, the pituitary produces luteinizing hormone (LH) which stimulates the seminal vesicles, but has no direct effect upon them. It merely causes another endo-

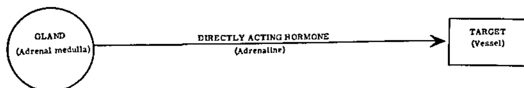
crine structure, the Leydig cells of the testis, to produce testoid hormones, which, in turn, exert a direct action on the target organ, the seminal vesicles. The gonadotrophic, thyrotrophic and corticotrophic hormones may all be cited as examples of such indirectly acting hormones, whose mediated effects depend entirely upon the integrity of the gonads, thyroid and adrenal cortex respectively.

It is for this reason that testosterone, a directly acting hormone, causes seminal vesicle growth in the castrate as well as in the intact male, while luteinizing hormone elicits this same response in intact animals, but is entirely ineffective following castration.

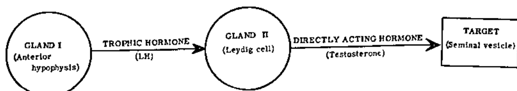
(3) CONDITIONALLY ACTING HORMONES. — These are directly acting hormones, whose effect upon the target organs is not dependent upon the integrity of any intermediate station. Yet, depending upon the circumstances, the receptive cells may or may not respond. Thus, for example, desoxycorticosterone acetate causes nephrosclerosis, but only if the diet of the experimental animals contains sufficient amounts of sodium and chloride. Similarly the direct actions of adrenaline can be modified by denervation which increases, or adrenolytic drugs which decrease the responsiveness of certain target organs to this hormone. To some extent, of course, all hormone actions depend upon the condition of the responsive cells. In some instances, however, the target is almost always optimally sensitive to the hormone, while, in others, the response is greatly influenced by activating or inactivating agents. These modifying agents may themselves be hormones. Thus progesterone, when given by itself, possesses only a very slight progestational effect upon the endometrium, but following pretreatment with minute doses of estradiol (or other folliculoid hormones), small doses of progesterone suffice to cause marked progestational reactions. On the other hand, pretreatment with very large doses of folliculoids completely inhibit the progestational action of the corpus luteum hor-

Mechanisms of hormone actions

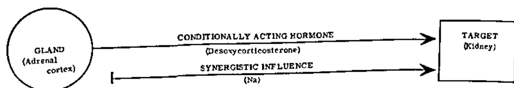
I- DIRECTLY ACTING HORMONE



II- INDIRECTLY ACTING HORMONE



III- CONDITIONALLY ACTING HORMONE



mone. Here, depending upon dosage, one hormone can both increase and decrease the response to another hormone.

In connection with the conditionally acting hormones, the following consideration is important, since disregard of it leads to many errors in the interpretation of observations. If a stimulus which normally causes a response in a target organ fails to do so after extirpation of an endocrine gland, this does not necessarily mean that its effect is mediated by that gland.

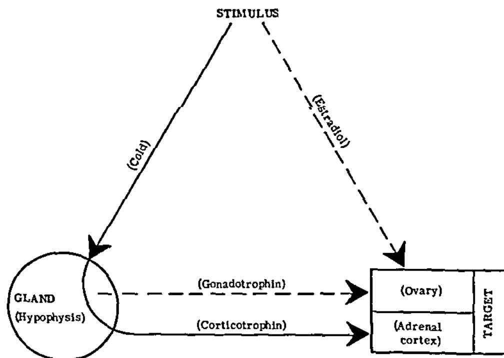
It must be kept in mind that if a stimulus cannot influence its normal target organ in the absence of an endocrine gland, there are two possibilities :

(1) The stimulus is an indirectly acting agent, which affects the target organ merely by modifying the hormone production of the endocrine gland in question.

(2) The stimulus is a conditionally acting agent, whose effect on the target organ depends upon simultaneous sensitization of the latter by a hormone produced by the endocrine gland in question.

Thus, exposure to cold causes adrenal-cortical enlargement in the rat, but only in the presence of the pituitary. Similarly, large doses of folliculoids elicit the production of large corpora lutea, but again only in the presence of the pituitary. An analysis of these two phenomena has shown that cold actually acts through the intermediary of the pituitary, causing it to produce an increased amount of corticotrophin. In hypophysectomized animals, exposure to cold leads to no cortical hypertrophy, even if their adrenals are maintained in a normal condition by daily corticotrophin injections. On the other hand, large doses of folliculoids, though ineffective in influencing the ovary of untreated hypophysectomized rats, cause enlargement of corpora lutea even after

Possible rôles played by an endocrine gland which is indispensable for the response of a stimulus



ablation of the hypophysis, if the ovary is maintained in an approximately normal condition by treatment with exogenous gonadotrophins. In this case, the folliculoids are conditionally acting agents, whose effect on the target organ (the corpus luteum) depends upon simultaneous sensitization of the latter by gonadotrophic pituitary hormones (mainly luteotrophin).

MECHANISM OF DIRECT HORMONE ACTIONS UPON TARGET ORGANS

Hormones are Merely Regulators of Biologic Phenomena. — Almost nothing is known as yet about the intimate mechanisms through which internal secretions influence their target organs. It becomes increasingly more evident, however, that hormones do not bring about any essentially new metabolic activity, but merely regulate the course of phenomena which can progress to some extent, even in their absence Thus, for example, thyroid hormone increases the basal metabolic rate, but in its absence, basal metabolism proceeds, although at a lower level; adrenotrophin stimulates the activity of the adrenal cortex, but some corticoid hormone production continues even after complete hypophysectomy; estradiol accelerates the proliferation of the vaginal epithelium, although in its absence, the lining cells of the vagina continue to grow at a greatly reduced rate Even the cornification of vaginal cells supposedly so specific of folliculoids (estrogens) is possible in their absence (e.g., in A-avitaminosis). *The effect of hormones has therefore often been compared with that of catalysts or enzymes,* whose function is likewise limited to the regulation of reactions which are essentially not dependent upon them. It has even been suggested that the hormones may actually be enzymes, but this has never been definitely demonstrated. The few pertinent data known at the present time would rather suggest that the hormones merely condition the activity of the enzyme systems which regulate biologic phenomena. Renin, however. is an enzymatic internal secretion of the kidney, which behaves like a conditionally acting hormone. It is inactive in itself but transforms certain blood globulins into the highly potent vasopressor substance hypertensin (or angiotonin).

Are hormones utilized while exerting their effects ?. After they enter the blood stream, hormones are partly destroyed in the body, due to chemical degradation or conjugation with other substances. *This yields inactive or less active end products;* hence the excretions (urine, feces, sweat, etc.) do not contain the total amount of the hormones produced by the endocrines. There is no definite proof, however, that hormones are actually "utilized" by the end-organs, that is, that they are consumed by the tissues as a result of their hormonal activity. Indeed, there is reason to believe that the destruction of hormones proceeds practically unchanged, even if they are prevented from exerting physiologic actions. Thus, the inactivation of exogenously introduced gonadotrophins is not significantly influenced by gonadectomy, although, in the absence of the gonads, these trophic principles can exert no physiologic action Perhaps the best proof for the relative independence of hormone destruction from hormone activity is the following .

If animals are completely deprived of endogenous gonadotrophins by hypophysectomy, their ovaries involute In *such animals, injection of gonadotrophic* hormones causes an ovarian enlargement which, at a certain range, is proportional to the amount injected Under such conditions however, the increase in the weight of one ovary is the same, whether the other ovary is present or not. If the gonadotrophic hormone were destroyed by the ovary itself (*while it performs its stimulating* action), obviously a greater effect should be obtained by a given dose

ARE HORMONES "UTILIZED" BY THEIR TARGET ORGANS WHILE THEY EXERT THEIR ACTIONS UPON THEM?

HYPOPHYSIS REMOVED						
"PAIRED GLAND" UNDER HYPOPHYSEAL CONTROL (e.g. OVARIES, THYROID, ADRENALS)						
UNITS OF TROPHIC HORMONE INJECTED	1 UNIT	2 UNITS	3 UNITS	1 UNIT	2 UNITS	3 UNITS
CONDITION OF PAIRED GLANDS	BOTH PRESENT			ONE PRESENT		

Note that the effect of trophic hormones is independent of the amount of target organ tissue present in the organism.

ablation of the hypophysis, if the ovary is maintained in an approximately normal condition by treatment with exogenous gonadotrophins. In this case, the folliculoids are conditionally acting agents, whose effect on the target organ (the corpus luteum) depends upon simultaneous sensitization of the latter by gonadotrophic pituitary hormones (mainly luteotrophin).

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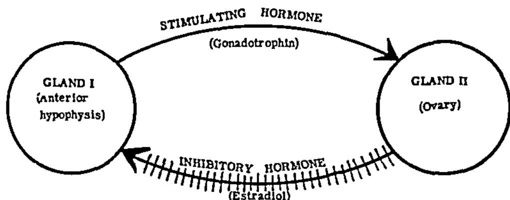
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cial instance of this mechanism. Some investigators believe that an increase in ovarian-hormone secretion automatically depresses the gonadotrophin secretion of the pituitary: since this is followed by a decreased ovarian hormone production, the gonadotrophin secretion is augmented during the next phase and so forth. (See : Sexual Cycle.)

The following drawings illustrate these mechanisms of compensatory hypertrophy and atrophy :

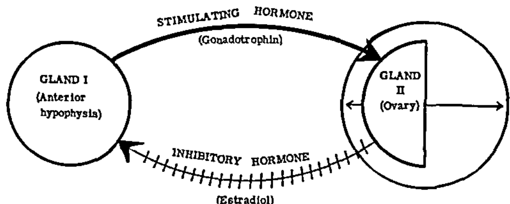
Compensatory hypertrophy and atrophy

I — Normal balance between glands I and II



The normal balance between gland I (e g, anterior-hypophysis) and gland II (e g, ovary) Gonadotrophin stimulates the ovary to produce estradiol which inhibits the anterior-hypophysis (Inhibition is indicated by cross-hatched arrows)

II — Effect of partial ablation of gland II



Following partial ablation of gland II the inhibitory-hormone production is diminished and hence an increased amount of stimulating-hormone is secreted by gland I, this leads to compensatory hypertrophy of gland II.

when only one ovary is present. Under similar experimental conditions, the adrenal enlargement caused by corticotrophin and the thyroid enlargement due to thyrotrophin proved to be independent respectively of the amount of adrenal and thyroid tissue present in the body. In animals whose hypophysis is intact, the removal of one gonad, adrenal or thyroid, causes compensatory hypertrophy of the contralateral gland. This, however, is not because the remaining glandular tissue benefits from an excess of trophic hormone due to non-utilization by the contralateral gland. It is due merely to the abovementioned compensatory hypertrophy mechanism, that is to say, if one of these paired glands is removed, the pituitary attempts to compensate by an increased production of the corresponding trophic principles. (See below.)

Hormones acting on many distinct target organs do not lend themselves well for similar studies. It has been found, however, that removal of the uterus and most of the vagina does not significantly influence the responsiveness of the vaginal remnant to a threshold dose of a folliculoid hormone, nor does ablation of most of the male accessory-sex-organs noticeably alter the sensitivity of the remaining sex-organs to a given amount of testoid material.

STIMULI REGULATING THE ACTIVITY OF ENDOCRINE GLANDS

Humoral and nervous stimuli help to adjust the activity of the endocrine glands to changing conditions in the organism or its surroundings.

Among the HUMORAL STIMULI, hormones play a particularly important rôle. Thus, the anterior-lobe of the pituitary is almost exclusively responsible for the normal function of the adrenal cortex, the thyroid, the gonads, and to some extent, even the Langerhans islets of the pancreas. All these endocrine glands are under the controlling influence of so-called trophic hormones of the anterior-lobe. Their name is derived from the Greek "trophe" = nourishment, although they are not nutrients in the ordinary (caloric) sense of the word. The anterior-pituitary has therefore been compared with the central nervous system, which plays a similar rôle in the integration of nervous activities. In order to adjust the function of the various "peripheral" endocrines to the needs of the organism, such a central control by one "master gland" is advantageous.

In order to stabilize the activity of those glands of internal secretion which are under hypophyseal control, the production of trophic hormones by the pituitary is in turn regulated by the peripheral endocrines. Thus, for instance, an increase in the gonadotrophin secretion of the pituitary augments the folliculoid hormone production of the ovary, but these folliculoids act back upon the pituitary to decrease its gonadotrophin secretion. In this manner the ovarian stimulation is maintained at a fairly steady level by a self-regulating mechanism. Such interrelations between the hypophysis and various peripheral endocrines are responsible for many of the phenomena of so-called *compensatory atrophy* and *compensatory hypertrophy*. Thus, thyroid hormone administration depresses the endogenous production of thyrotrophin by the anterior-lobe and causes a compensatory atrophy of the thyroid; partial thyroidectomy and the consequent decrease in circulating thyroid hormone acts as a stimulus for the compensatory increase in thyrotrophin production and thus, helps to re-establish a normal thyroid hormone concentration in the blood through the stimulation of the thyroid remnant Many other examples of compensatory atrophy and hypertrophy will be mentioned in the sections devoted to the individual endocrine glands. Indeed, the menstrual cycle may merely represent a spe-

hormonal causation of a change (e.g., testicular atrophy) or the hormonal nature of a biologic substance (e.g., pituitary extract).

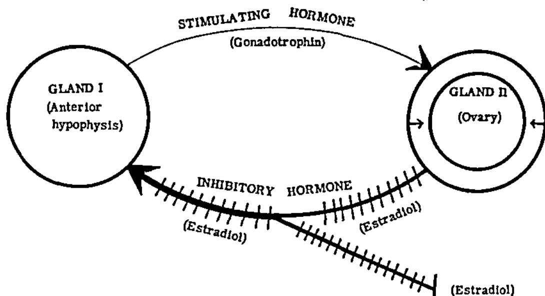
Extirpation Causes Deficiency. — One of the most important proofs for the endocrine activity of an organ is that its surgical removal causes specific deficiency symptoms. This is due to the fact that most hormones are produced in one organ only, so that after complete destruction of the latter, hormone production ceases. Thus, after extirpation of the testes, there is involution of the seminal vesicles, prostate and other male accessory-sex-organs, because only the testis produces significant amounts of testoid (androgenic) hormones. Similarly, removal of the hypophysis induces gonadal, adrenal-cortical and thyroid atrophy, since only the trophic hormones of the pituitary have the ability to stimulate these glands directly It becomes increasingly more evident, however, that the organ specificity of hormone production is by no means an absolute rule. Thus, certain amounts of hypophysoid (gonadotrophic, luteotrophic) and folliculoid hormones can be produced by the placenta, testoids by the adrenal cortex, etc. Some organs elaborate hormones which can also be secreted by other tissues Therefore, if extirpation of a gland does not cause any specific deficiency symptoms, this should not be interpreted as absolute proof against its endocrine nature. For instance, the impossibility of producing specific signs of deficiency by thymectomy or pinealectomy can not be regarded as absolute proof against their hormone-producing ability

If in such instances complete extirpation of all endocrine cells is impossible, the production of similar hormones by several organs must be proven by the procedures mentioned below (e.g., specific overdosage symptoms by glandular extracts, demonstration of hormone in the venous blood of the gland, proof that the hormone concentration in the body and its excretions depends upon the degree of development of the supposedly endocrine tissues, etc.).

Organ Extract Causes Overdosage. — After suitable purification and concentration, the active principles of endocrine organs can be shown to possess physiologic activities, similar to those normally exerted by the organ itself. Indeed, if excessive doses of such preparations are injected into experimental animals, usually hormone-overdosage results. This procedure lends itself even for the demonstration of endocrine activity in tissues which, for technical reasons, cannot be completely eliminated and hence do not lend themselves to proof of their internal secretion by the production of an experimental hormone-deficiency.

In evaluating the results of such experiments, it must be kept in mind, that although large amounts of hormones are secreted by certain tissues, their active principles are not necessarily stored to any extent in the cells which elaborate them Under such conditions, it may be very difficult to obtain the necessary concentration of hormone activity in gland extracts. For instance, the ovaries contain only negligible quantities of folliculoid hormones, so that crude ovarian extracts reveal themselves as inactive in tests of this type. On the other hand, if a definite biologic activity is demonstrated in an organ extract, this does not prove that the tissue normally secretes such principles into the blood Various active metabolites accumulate in cells and a variety of poisons prepared from the organs of animals or plants can act as drugs. Their activity does not necessarily bear any direct relationship to the normal physiologic function of the tissues from which they were obtained. It is for this reason that the effect of organ extracts, injected into intact test animals, must simulate the normal physiologic function of the tissue from which they are

III — Effect of exogenously introduced hormone of gland II



Exogenous administration of the inhibitory-hormone (e g, estradiol) causes inhibition of gland I and thus diminishes the stimulating-hormone production, this leads to compensatory atrophy of gland II.

Many OTHER HUMORAL AGENTS exert a regulating influence upon the secretion of the endocrines. Thus glucose increases the production of insulin, while hypoglycemia causes a discharge of adrenaline Since insulin depresses while adrenaline raises the blood sugar level, these responses are eminently suited for the self-regulation of the blood sugar level.

NERVOUS STIMULI likewise play an important rôle in the regulation of hormone production. For example, stimulation of the splanchnic nerve causes adrenaline liberation apparently because this nerve contains secretory fibers regulating the hormone production of the adrenal medulla Similarly, the nervous stimulus of nursing has been proven to regulate the secretion of prolactin by the hypophysis, thus adjusting the amount of milk produced to the requirements of the nursling. The hormone production of many endocrine glands, however, is remarkably independent of nervous stimuli, for instance complete denervation of the parathyroids, thyroids, adrenal cortex and gonads causes no significant change in their ability to secrete hormones or even to adjust the quantity of their hormone production to varying requirements.

In summary it may be stated that the elaboration of hormones is mainly dependent upon · 1) the amount of circulating hormones in the blood, 2) the blood concentration of certain metabolites whose utilization depends upon hormones, 3) nervous mechanisms

CLASSIC EXPERIMENTAL PROCEDURES IN ENDOCRINOLOGY

PROOF OF ENDOCRINE ACTIVITY OF AN ORGAN

A series of experiments has to be performed to prove the endocrine activity of an organ. Only in a few cases is it technically possible to furnish all the proofs enumerated below, but generally, the three first-mentioned procedures are accepted as giving adequate information It will be borne in mind that essentially the same type of experimental evidence is necessary to establish the

gland can be shown to secrete biologically demonstrable quantities of thyroid hormone into the perfusion fluid.

Isolation of the Pure Hormone — The best proof for the endocrine activity of an organ is the isolation of its pure hormone or hormones. This can be accomplished by chemical or physical means. The pure product is usually a crystalline, physically homogenous substance which accurately imitates the normal endocrine activity of the organ. In intact animals, it simulates the endocrine activity of the gland by producing overdosage effects, while in animals rendered deficient in the secretions of the gland (e.g., by extirpation) it gives complete substitution therapy. Non-protein hormones usually form typical crystals, whose melting point, crystal form, optic rotation, etc., help to identify them (e.g., steroid hormones, adrenaline, thyroxin). The crystallization of protein hormones (e.g., insulin), is difficult, however, and in itself not a conclusive criterion of purity. Usually, homogeneity can only be demonstrated by several physical constants, for instance osmotic pressure, solubility, electrophoresis, etc. (e.g., growth hormone, prolactin)

PROOF THAT A SYNTHETIC SUBSTANCE IS IDENTICAL WITH THE NATURAL HORMONE

It has been possible to synthesize several hormones. In order to demonstrate that such synthetic compounds are actually identical with the naturally occurring hormones, it is essential to show that they imitate all biologic and chemical actions of the latter. In the case of crystalline substances (e.g. steroids), the melting point of the artificial compound must be identical with that of the hormone prepared by extraction and purification of glandular tissue; even after mixing the artificial and natural substances, the "mixed melting point" must remain the same. Synthetic protein-hormones have not yet been prepared.

PRINCIPLES OF BIOASSAY

It is not within the scope of this book to give a detailed account of bioassay technics or of the mathematical principles upon which we base their interpretation, but the following fundamental considerations are indispensable.

Purely technical reasons often preclude the use of accurate, sensitive and specific chemical tests for the estimation of hormone concentrations in biologic materials. In such instance the hormones are better identified and estimated on the basis of their biologic activities.

In principle, we may distinguish between "internal" and "external" bioassays. INTERNAL BIOASSAYS are based upon the observation of target organs in the individual whose hormone production we wish to estimate. Thus, vaginal smears or uterine biopsies taken from a woman are internal indicators of her own ovarian-hormone production. In certain instances, the responsiveness of such internal indicators can be increased by special sensitizing methods. Thus, the responsiveness of the iris, or the heart, to endogenously produced adrenaline is augmented by denervation.

All these internal bioassay methods have the advantage that no loss of hormone is incurred, since they require no extraction from the tissues of the donor or transfer to a recipient test animal. They are simple technics in which the hormone production of the same individual can be repeatedly tested under identical conditions and they give an over-all picture of the effective hormone concentration in the body. They lend themselves well to serial determinations of the endogenous hormone production of an individual under varying conditions.

Their great disadvantage is that they are less suitable than external bioassays

derived before the experiment can be interpreted as indicative of endocrine activity.

Efficacy of Substitution Therapy. — It is a particularly convincing proof of the endocrine activity of tissues if extracts prepared from them can correct the deficiency symptoms produced by extirpation of the organ in question. Such "substitution therapy" shows most clearly that the extracts truly *imitate the physiologic function of organs.*

The classic procedure is to remove an endocrine gland from an experimental animal, note the resulting deficiency syndrome, and then restore conditions to normal by the administration of purified organ-extract concentrates.

For instance, the atrophy of the accessory-sex-organs subsequent to castration, is restored by the administration of active testicular extracts. This type of proof is again not applicable in the case of endocrine organs which cannot be removed, completely enough, to produce a definite deficiency syndrome.

Demonstration of Hormone in Venous Blood of Endocrine Organ. — In certain instances, it is actually possible to demonstrate a high concentration of hormones in venous blood coming from an endocrine organ. This is significant only if the concentration in the veins of the endocrine organ is much higher than in the general systemic circulation

Thus, unusually high concentrations of adrenaline or corticoids have been demonstrated in the adrenal veins by direct bioassay. This experimental procedure is particularly suitable for *the study of changes in hormone secretion* induced by various stimuli (see below). It has been shown, for instance, that the adrenaline concentration in the *adrenal veins is increased after splanchnic* stimulation, insulin administration, emotional stimuli, etc. From this it could be concluded that probably a discharge of this hormone also occurs physiologically under the direct influence of such stimuli.

Demonstration that Hormone Concentration in the Body and Excretions Depends upon the Condition of the Endocrine Organ. — Dependence upon an organ of the hormone concentration *in the blood, the tissues and excretions,* may help to identify it as a hormone producer. Thus, partial or complete *extirpation of a gland* or its *destruction by disease* decreases, while *stimulation of its activity* (by trophic hormones, nervous stimuli and other agents) demonstrably increases hormone production, approximately in proportion with the amount of glandular tissue present

Other technics may help to demonstrate that a biologic change depends upon the presence of certain endocrine cells in the organism: among these are, *transplantation* of endocrine organs (in the form of free grafts or by anastomosis of the transplant's vessels with those of the host), or the establishment of a *cross-circulation* or *parabiosis* between the body of an animal in which an endocrine gland has been removed, with a second animal in which this gland is present.

Explantation of endocrine cells (tissue cultures) may reveal the formation of hormones by the cells in vitro: similarly in organ cultures (perfusion of isolated endocrine glands) *hormonal principles* can be elaborated and secreted into the perfusing fluid, where they become demonstrable by bioassay or chemical tests

After gonadectomy for instance, the concentration of gonadal hormones in the blood and urine can be shown to diminish; *transplantation of the gonads* into gonadectomized hosts restores conditions to normal and cross-circulation or parabiosis between a gonadectomized *and a normal animal reveals the transition* of gonadal hormones from the latter to the former. Similarly, thyroid cells produce thyroid hormone in vitro *and if a whole thyroid* is perfused, the

dose levels is not very different within the initial and final flattened portions of such curves. It is advisable to transform the original sigmoid curve into a straight line, since the usual statistical computations assume that over the dosage range used, the dose-response relationship follows a straight line.

If the test is based on a *"yes or no" response* (e.g., number of deaths in toxicity tests, number of animals showing cornified smears in folliculoid assays), this can be accomplished by plotting the log of the dose against the probit of the response. Convenient tables have been prepared for this purpose.

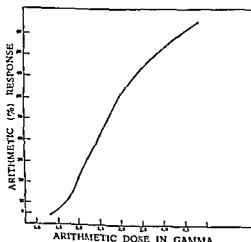
Other types of bioassays give *graded responses*, that is, even among the positive reactors, the degree of response *depends upon the amount of hormone* administered (e.g., adrenal weight in the assay of adrenotrophic hormone, duration or depth of anesthesia in the assay of anesthetic steroids). In these instances, the dosage-response curve can be transformed into a straight line by plotting the dose against the arithmetic response. Sometimes, however, the log or some other function of the response, must be used to fit the desired relationship over the dosage-range in question

The following two examples, based on actual bioassays (courtesy of Dr. L. Pugsley), illustrate these points. The first gives the data and curves of an estrone assay (vaginal cornification), the second of an androsterone assay (capon-comb growth):

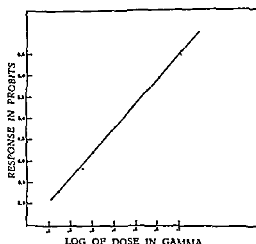
Dosage-response data for Estrone using castrated female rats

No of rats	Dose (in γ)	Log dose	Response (in %)	Response Probits
25	1.4	.1461	4	3 2493
25	1 8	2553	12	3 8250
23	2 0	.3010	22	4 2278
26	2 5	.3979	42	4 7981
26	3 0	.4771	62	5 3055
25	4 0	6021	84	5 9945
22	5 0	6990	95	6 6449

Dosage-response curve of Estrone
(quantal response)
Arithmetic dose against arithmetic response



Dosage-response line of Estrone
(quantal response)
Log arithmetic dose against probit response



for exact quantitative determinations on a statistically significant basis. Furthermore, they give no indication concerning the distribution of the hormone in the various body fluids and tissues.

Conversely, the EXTERNAL BIOASSAYS are based upon the removal from a donor, of certain specimens of body fluids or tissues, which are tested by their effects on other animals. They can be administered as such, or after suitable purification and concentration of the active material.

It is advisable, furthermore, to USE MODERATE DOSES for bioassay purposes, that is, quantities just sufficient to produce a definite biologic reaction. If large quantities are given, the relationship between the dose injected and the result obtained is less definite, while threshold doses give erratic results.

In all bioassay technics, it is important to ADMINISTER THE HORMONE IN A MANNER ASSURING GOOD ABSORPTION, with as little destruction as possible (see: Technics of Hormone Administration, below).

In selecting a suitable test object it is noteworthy that ANIMALS DEFICIENT IN A CERTAIN HORMONE ARE USUALLY *MOST SUITABLE for the bioassay of that* hormone. If adequate amounts of a hormone are present in the body, the addition of small doses fails to cause a significant change For this reason, the folliculoid hormones are assayed on spayed or immature animals which have no significant endogenous source of such hormones. For similar reasons, hypophyseal hormones show their activity much better in hypophysectomized than in intact animals The use of animals deprived of the specific endocrine gland in question is also advisable since compensatory changes due to endogenous hormone production cannot take place during the bioassay and hence, the effect of the injected hormones is not blurred by internal adaptive mechanisms.

CONDITIONALLY ACTING HORMONES SHOULD BE TESTED UNDER CIRCUMSTANCES MOST FAVORABLE FOR THE EXERTION OF THEIR EFFECTS. Thus insulin, whose hypoglycemic action is largely dependent upon dietary factors, should be assayed in fasting animals; progesterone in animals sensitized by folliculoids, etc.

Hormones to which ADAPTATION (e.g., progesterone), TACHYPHYLAXIS (e.g., vasopressor posterior-lobe extracts) or ANTI-HORMONE FORMATION (e g., hypophysoid gonadotrophins) occurs, *must be assayed on animals not* desensitized by previous treatment. Very PROLONGED HORMONE DEFICIENCY MAY RENDER ANIMALS COMPARATIVELY INSENSITIVE to certain internal secretions. This must be taken into account for instance in the assay of folliculoids on rats spayed long before the test. In such cases a single injection of folliculoids a few days before the test, usually suffices to restore normal responsiveness.

It is advisable to COMPARE THE ACTIVITY OF THE UNKNOWN HORMONE CONCENTRATION WITH THAT OF A MEASURED STANDARD PREPARATION, under similar laboratory conditions. Interna*tional standards of pure hormone prep*arations have been established by the League of Nations and samples of these are placed at the disposal of interested investigators.

In general, it is best to base bioassays on the determination and use of a DOSAGE-RESPONSE LINE. For this purpose, at least three dosage levels must be tested, since it requires at least three points to define a line, with which the points obtained by individual determinations can subsequently be compared. With most bioassay procedures, sigmoid curves are obtained when the arithmetic dose is plotted against the arithmetic response. The dose level at which the tests are performed should fall within the steepest portion of the curve, because the response to varying

ual results in single tests, while the latter raise or depress the average response of the entire group receiving the same hormone treatment.

In connection with the statistical evaluation of any biologic finding it is important to emphasize that these can only tell us whether the difference between two groups of results is significant or merely apparent. Thus, if in studying the growth-inhibiting effect of folliculoids most, but not all, the treated animals are smaller than their controls, statistical evaluation of the results can tell us whether the growth inhibition was real or not. It cannot tell us, however, that folliculoids inhibit growth. In the above example it could be possible that the animals treated with the folliculoids were unwittingly also injected with some toxic or infectious material, which was accidentally introduced into the solution, or that their growth was inhibited due to a latent infectious disease, prevalent in their cage but not in that of the controls, etc.

Many serious abuses of statistical evaluation, not only of bioassays but also of other scientific observations, are due to the tendency of experimenters to disregard these self-evident facts and to imply that the evaluation of their data, and not the data themselves, is supported by statistical analysis.

Conversely, it must be kept in mind that lack of statistical significance merely means that we can not prove that our observation *is not* due to chance; this does not mean that we proved it is due to chance. Furthermore, not every type of observation must be "statistically significant" in order to be important. Thus single case-reports of rare diseases can be very instructive, although the changes depicted do not lend themselves to statistical analysis. To illustrate this point by a simple, although fantastic, example — if only a single animal would indefinitely survive complete hepatectomy, all our current theories of intermediate metabolism would have to be revised, although the observation would not be statistically significant.

TECHNICS OF HORMONE ADMINISTRATION

Route of Administration. — The route of administration exerts a considerable influence upon the activity of hormone preparations. Certain hormones (e.g., insulin, vasopressin, oxytocin, parathyroid hormone, etc.) are ineffective when given BY MOUTH, while others (e.g., thyroid hormone, certain folliculoids and corticoids) are highly effective by this route. Ineffectiveness following oral administration is probably due in some cases to destruction by the digestive enzymes of the gastrointestinal tract, in others, to inactivation by the liver to which orally given hormones are carried directly through the portal vein.

As regards parenteral administration of hormones, it may be said that INTRAVENOUS injections are most rapidly effective, but generally exert more transitory effects, than INTRAMUSCULAR and SUBCUTANEOUS injections.

Certain hormones which are comparatively ineffective when given orally may be administered by direct application to MUCOUS MEMBRANES. In a sense, this is a procedure intermediate between the oral and the intravenous route of administration. From the oral, nasal or tracheal mucous membranes, certain hormones (e.g., adrenaline, steroids, posterior-lobe hormones) are comparatively readily absorbed without much local destruction by the surface epithelium.

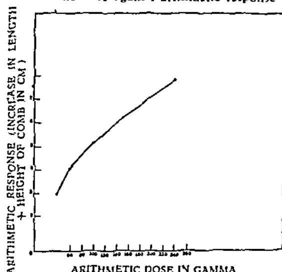
Several hormones are readily absorbed through the SKIN (e.g., estradiol, testosterone), but this route of administration is rarely indicated since it is wasteful and does not permit accurate dosage.

Comparatively large amounts of certain hormone preparations can be rapidly absorbed from the PERITONEUM.

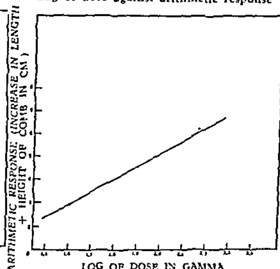
Dosage-response data of Androsterone, using Capons

No. of capons	Dose (in γ)	*Log dose*	Response Length and Height of comb in cm
10	40	1 6021	2 9
10	60	1.7782	4 0
10	100	2.000	5 1
10	150	2 1761	6.2
10	250	2 3979	7 8

Dosage-response line of Androsterone
(*graded response*)
Arithmetic dose against arithmetic response



Dosage-response line of Androsterone
(graded response)
Log of dose against arithmetic response



In the case of hormone preparations for which no international standards are available, it is necessary to express the results of bioassays in terms of arbitrary UNITS. Whenever possible these units are expressed as equivalents of a certain weight of the crystalline pure hormone. Thus, one international unit of luteoid activity corresponds to 1 mg of pure crystalline progesterone, the international unit of testoid activity is 100γ of androsterone: the international unit of folliculoid activity is 0 1γ of estrone, etc.

Finally, it is indispensable that the results of the bioassays be subjected to ANALYSIS BY SUITABLE STATISTICAL METHODS. For this, it is indispensable that the variations in the individual assays be expressed as the "standard deviation" or one of its modifications It does not suffice to indicate the range and mean of the individual results, since this precludes the possibility of a QUANTITATIVE MEASUREMENT OF THE VARIATION.

In biologic assays we encounter two types of variation The *individual variations* are due to the fact that various animals of the same species do not respond in exactly the same manner when exposed to the same treatment. *Aperiodic variations* are those which affect entire groups of animals of the same species, at irregular time intervals. The former are frequently due to hereditary factors, diseases, etc , which affect individual animals, the latter to irregular variations in temperature, diet, climate, season, etc., which affect the entire group of test animals The former increase the standard deviation of individ-

is increased and more hormone can be assimilated than from pellets, yet the absorption rate remains continuous. If aqueous suspensions are administered, the solvent is rapidly absorbed and the minute hormone deposits come into direct contact with the tissues. In the case of oily suspensions, only a few particles are in actual contact with the absorbing tissues and the mechanism of hormone uptake is somewhat different. In this case, the suspended particles merely assure that the hormone concentration in the oil always remains near the saturation point, in spite of selective absorption of that portion of the hormone which is in solution.

Activation and Inactivation. — Certain hormone preparations become more effective if administered in the form of their ESTERS. Thus, testosterone propionate is more active than testosterone, mainly because hydrolysis of the propionate progresses slowly and hence, esterification delays and prolongs the activity of a single injection. In other instances, esterification activates the hormone because it increases its resistance to destruction when administered orally. Thus, estrone sulfate is more active than estrone when both are given by mouth.

Other hormones are activated by ADMIXTURE OF CERTAIN SUBSTANCES, without there being any actual compound-formation between the hormone and the activator. Thus, when given simultaneously, certain heavy metals augment the activity of gonadotrophic preparations, zinc increases the effect of insulin, etc. Some hormones are activated by other hormones. In the previously cited instance of progesterone, for instance, pretreatment or simultaneous treatment with folliculoids results in a great increase in activity. Somewhat confusingly, this type of activation has often been described as "sensitization" (see below).

Sensitization and Desensitization. — The term "SENSITIZATION" is employed to describe an increase in sensitivity, following pretreatment with the same hormone principle. It has been found for instance that some time after spaying, rats loose a great deal of their sensitivity to folliculoid hormones, but a single folliculoid hormone injection suffices to re-sensitize them. This sensitization should be distinguished from the cumulative effect of certain hormone preparations The latter is merely due to the fact that threshold doses of a slowly acting hormone may not elicit any detectable action in themselves, but if several such doses are administered consecutively, a sufficient hormone concentration is gradually built up in the body to elicit a manifest change. Thyroid hormone, which exerts its actions very slowly, is subject to such cumulative effects following chronic administration. This must be taken into account in determining the adequate dosage for the hormonal treatment of hypothyroidism, since quantities ineffective during the first days of treatment may actually result in overdosage phenomena after sufficient time has elapsed for the cumulation of their actions.

Conversely, DESENSITIZATION to hormone preparations may be accomplished by previous treatment with the same substances In certain instances, a single injection of a hormone is rapidly followed by brief periods of comparative insensitivity, which has been described as *"tachyphylaxis."* The mechanism of this phenomenon has not yet been fully explained. It may be due to a temporary refractoriness of the target organ, or to a depletion of the body in necessary "co-hormones" or activators, which are essential for the activity of conditionally acting hormones. Vasopressin tachyphylaxis is probably due to the first-mentioned mechanism, while the ineffectiveness of renin, following repeated injections, is presumably due to depletion of the reninactivator (blood-globulin).

ANTI-HORMONE formation to certain endocrine products may also lead to desensitization, as we shall see in the chapter devoted to the anti-hormones.

In some cases the mechanism of desensitization is not known and then the phenomenon is usually designated by the non-committal term of "ADAPTATION" Thus, the somatic-growth-inhibiting effect of moderate doses of folliculoids in the rat, or the sex-skin stimulation by the same hormones in certain monkeys, vanishes after a period of continuous treatment. We do not know, however, through what mechanism this adaptation is effected

Therefore, in the case of water-insoluble hormones, intraperitoneal administration may be the most effective *means of ascertaining a sudden and* very pronounced increase in the hormone concentration of the blood. This was the basis for the intraperitoneal administration of the water-insoluble steroids for anesthetic purposes. The sudden and pronounced rise in blood steroid concentration necessary for the production of anesthesia is difficult to *obtain by* other means.

The DIRECT APPLICATION OF HORMONES TO THEIR TARGET ORGANS is especially advantageous, when an exclusively local action is desired. Thus, adrenaline is applied directly to wounds in order to decrease bleeding through its local vasoconstrictor effect; similarly, testosterone applied directly to the capon's comb causes an increase in the weight of this accessory-sex-organ, without influencing the other secondary sex-characteristics of the bird.

The local administration of hormone preparations has the additional advantage that comparatively small doses suffice to produce definite effects. This has often been used to advantage in bioassay technics. Thus, extremely small doses of luteoid hormones can be detected, by the local progestational proliferation in the rabbit endometrium, when they are directly applied to it.

The Solvent. — The solvent in which a hormone is parenterally administered plays an important rôle in determining its efficacy. Certain hormones *are much more rapidly absorb*ed than the solvents in which they are given and since it is time-taking for the organism to extract the hormones selectively from their solvents, activity is delayed by slowly absorbable solvents. It has been shown that the folliculoids (as well as other steroids) can be absorbed selectively from oil, since the *hormone* concentration of the parenterally administered oil gradually decreases before the solvent disappears completely. It is because of this that estrone sulphate given subcutaneously, in aqueous solution, has a much more *rapid and evanescent effect than* when it is given in oily solution. For intravenous administration, only aqueous solutions are to be recommended. Certain water-insoluble steroids have been administered intravenously in other solvents (e.g., glycols), but this is inadvisable, since after dilution with serum, such solutions become unstable and the *hormones tend to precipitate. This* introduces the danger of hormone-embolisms.

Pellets and Suspensions. — If delayed and very continuous hormone absorption is desired, compressed PELLETS of hormone crystals can be implanted under the skin. The compounds are gradually absorbed from the surface of such pellets and this assures a continuous, steady hormone supply. In cases of eunuchoidism, testoids; in Addison's disease corticoids, have advantageously been administered in this manner. This saves the patient the annoyance of continuous injections and at the same time, reduces the cost of treatment, since comparatively small amounts of hormone suffice to produce a definite effect under these conditions. It must be kept in mind that in the case of repeated hormone administration in readily absorbable form, a great deal of the hormone is wasted, because at certain times, the blood concentration of the substance is excessive and much of it is lost through the excretions, or through *excessive destruction in the tissues.* Between injections, on the other hand, the hormone concentration tends to fall below the effective level.

The administration of SUSPENSIONS of crystalline or amorphous hormone preparations in fluids in which they are not soluble, represents a modification of the pellet-implantation technic. Its advantage is that by introducing a large number of comparatively small hormone particles, the absorption surface

is increased and more hormone can be assimilated than from pellets, yet the absorption rate remains continuous. If aqueous suspensions are administered, the solvent is rapidly absorbed and the minute hormone deposits come into direct contact with the tissues. In the case of oily suspensions, only a few particles are in actual contact with the absorbing tissues and the mechanism of hormone uptake is somewhat different. In this case, the suspended particles *merely* assure that the hormone concentration in the oil always remains near the saturation point, in spite of selective absorption of that portion of the hormone which is in solution.

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Commercial Hormone Preparations

(Compiled with the kind assistance of Miss Helen Stone, Montreal, Schering Corporation, Bloomfield, New Jersey, *Roche Organon* Nutley, New Jersey and Frank W Horner Limited, Montreal).

The following is a list of commercially available endocrine products and their distributors However, almost continually, some products are taken off the market while others are added, hence the list is *necessarily incomplete* It is given here mainly to help physicians to identify hormone preparations whose trade-name is not self-explanatory

I — ADRENALINE

Epinephrine (U S P XIII)
Adrenalin (Parke Davis)
Adrin (Sharp & Dohme)
Biosurrenal (Instituto Opoterapico Nazionale)
Endiphein Inhalant (Harrower)
Epinephrine (Wilson)
Epinephrine HCl (Abbott, Biorganic, Boyle Breon, Bristol Buffalo Burroughs Wellcome, Chicago Pharm Denver Mud Endo Estro Gold Leaf Gotham Grant Harrower, Hart *Ingram* *Kremers*-Urban Lakeside Lederle Massengill McNeil, Merrell Metropolitan Miller National Drug Phys Drug Picker, Premo C D Smith Smith-Dorsey Solex Supreme U S Standard Upjohn, Warren-Teed Winthrop)
Supranephrin (Rorer)
Suprarenalin (Armour)
Suprarenin (Winthrop)
Tonhormon (Byk-Gulden)

II — ADRENAL CORTICAL HORMONES

A DESOXYCORTICOSTERONE ACETATE

Desoxycorticosterone Acetate (U S P XIII)
Cortate (Schering)
Cortenil (Farben)
Cortiron (Schering)
Doca (Roche-Organon)
Neocortine (Godeau)
Percorten (Ciba)
Syncortyl (Herman-Labor)

B ADRENAL CORTEX EXTRACTS

Adrenal Cortex (Armour Bellevue, Breon Christina Endo Estro Harrower Lakeside Marvell Pitman Moore Prof Prod Smith-Dorsey Upjohn, Wilson)
Adrenal Cortical Ext (Connaught)
Adreno-Cortin (Endocrine Harrower)
Adrenofer (Istituto Opoterapico Nazionale)
Cortalex Tabs (Upjohn)
Cortedrin (Harvey)
Cortical C (Istituto Opoterapico Nazionale)
Cortical Extract (Gold Leaf Kremers Urban United Labs)
Cortidyn (Kretschmer)
Cortin (*Degewop Roche-Organon*)
Cortine Naturelle (Laroche-Navarron)
Cortinoral (Harrower)
Cortisorbate (Reed & Carnrick Schieffelin)
Cortithurin (Harrower)
Eschatin (Parke Davis)
Glycortal Pills (Schieffelin)
Interrennin (Marvell)
Lipo-Adrenal Cortex (Upjohn)
Novocortex (Iscovesco)
Suprarenal Cortex (*Armour* Burroughs Wellcome Carnrick Lafayette Massengill Miller Pro-Medico Upjohn U S Standard Wilson)

III — ANTERIOR PITUITARY HORMONES

A THYROTROPHIC HORMONE (THYROTROPHIN)

Pretiron (Schering)
Thyractin (Winthrop)
Thyrogan (British Drug Houses)
Thyrotropic Factor (Armour Averst McKenna & Harrison)

B ADRENOTROPHIC HORMONE (CORTICOTROPHIN)

Adrenotrophic Factor (Armour, Ayerst McKenna & Harrison)

C. SOMATOTROPHIN AND PREPARATIONS CONTAINING SEVERAL ANTERIOR LOBE PRINCIPLES IN COMBINATION WITH SO-*MATOTROPHIN*

Accretin (Harrower)
Antuitrin-G (Parke Davis)
Growth Complex (Armour)
Growth Factor (Averst, McKenna & Harrison)
Phyone (Wilson)
Pituitary Extract S' Fraction (Miller)

D LACTOGENIC HORMONE (PROLACTIN, *LUTEOTROPHIN*)

Praelacton (Promonta)
Prolactin (Armour Ayerst McKenna & Harrison, Schering Squibb)
Suppletan (Boehringer)

E HYPOPHYSEAL GONADOTROPHIC EXTRACTS

Accretin (Harrower)
Ambinon (Roche Organon)
Antelobine (Byla)
Anterior Pituitary Ext (*Alpinol A P C* Armour, Bellevue Bishop Breon Buffalo Cole Direct Sales, Empire Endo Ennes Estro Fitch Flint Eaton, Gotham Haist, Harrower Harvey Pittenger, Ingram Kirk, Lakeside Lilly Marvell Massengill, Maurry McNeil Metropolitan Miller National Drug Parke Davis, Park Drug, Phys Drug, Pitman-Moore Premo Prof Prod Pynosol Sharp & Dohme Sherman C D Smith Smith-Dorsey, Squibb United Labs United Standard Upjohn, Verax Vitarine)
Antex Leo (*Lovens Kemiske Fabrik*)
Anteparsine (Gremy)
Antrone (Endo)
Entridin (Endo)
Entromone (Endo)
Equiphysin (Harvey)
Gonadophysin (Searle)
Gonadothyn (Flint Eaton)
Gonado Trone (Miller)
Gonadotrope (Forbes Straub)
Gonadotrophin Factor (Armour Ayerst McKenna & *Harrison Kirk Premo*)
Gonatrin B (Spanner)
Gynantrin (Searle)
Hormogen-S (Mallard)
Lutrogen (Difco)
Megalin (Difco)
Phykentrone (Squibb)
Physex Leo (Lovens Kemiske Fabrik)
Pituitary Gonadotrophin (Squibb)
Pituitras C (Verax)
Polyansyn (Armour Averst McKenna & Harrison)
Prephysin (Chappel Stearns)
Synapoidin (Parke Davis)

F CHORIONIC GONADOTROPHIN (ANT PI-*TUITARY-LIKE EXTRACTS HYPOPHYSOID* HORMONES OF PREGNANCY URINE OR PLACENTA)

Antregone (Abbott)
Antuitrin-S (Parke Davis)
Apestrin (Harrower)
Apitor (*Estro*)
A P L (Averst McKenna & Harrison)
Anterior Pituitary Like Hormone (Bellevue Bishop Pynosol U S Standard)
Asprodin (Smith-Dorsey)
Choranid (Smith)
Chorcomon (Mack)
Chorgon (Massengill)
Choriogonin (Lakeside)
Chorione (Hospital Liquids)
Chorionex (Horton & Converse)
Chorionic Gonadotrophin (Armour, Bellevue Breon Cole Empire Drug Endo Estro Hygiene Inc Kirk Lakeside Maurry McNeil Pitman Moore Prof Prod Upjohn United Labs U S Standard)

Choriotropin (Metropolitan Lab)
Follutein (Squibb)
Gestasol (National Drug)
Glantropin (Ingram)
Gonadithyn (Flint Eaton)
Gonan (British Drug Houses)
Gonatris B (Spanner)
Korotrin (Winthrop)
Lyorac Vasales (Sharp & Dohme)
Marvantrine G (Marvell)
Neo Apoidin (Parke Davis)
Placentrin (Italian Drug)
Prachormon (Promonta)
Prastucon (Schering)
Pregenyl (Degewop)
Pregnyl (Roche-Organon)
Prolan (Farben)

G EQUINE GONADOTROPHIN (PREGNANT MARE SERUM)

Anteron (Schering)
Antex (Ayerst, McKenna & Harrison)
Apoidine (Parke Davis)
Gestyl (Roche Organon)
Gonadin (Cutter)
Gonadogen (Upjohn)
Serogan (British Drug Houses)

IV – POSTERIOR PITUITARY HORMONES

A. PRESSOR-PLUS OXYTOCIC FACTORS

Posterior Pituitary (U S P XIII)
lo)
Infundin (Burroughs Wellcome)
Pitone (N V Organon-Oss)
Pituitrin (Parke Davis)
Post-Hypophyse (Choay)
Posterior Pituitary desic (Armour Lilly Parke Davis Wilson)
Posterior Pituitary Extract (Abbott A B C Alpinol Armour Bellevue Bishop Blue Line Breon Bristol Buffalo Cheplin Chicago Pharm Christina, Cole Endo Estro Flint Eaton Frosst Gold Leaf Halst, Harrower Harvey Horton & Converse Ingram Intra Prod Kremers-Urban Lakeside Lilly Mallard Marvell Massengill McNeil Merrell Metropolitan Miller National Drug Parke Davis Phys Drug Pitman Moore Premo Prof Prod Rorer Sharp & Dohme Sherman C D Smith Smith Dorsey Soler Squibb Torigian Tosse United Labs, Upjohn, U S Standard Veras Vitarine Warner Warren-Teed Wilson Wyeth)
Posterior Pituitary Ob & Surg (Miller)

B PRESSOR FACTOR (β-HYPOPHAMINE VASOPRESSIN)

Pitressin (Parke Davis)
Pitressin Tannate (Parke Davis)
Tonephin (Farben)
Vaso-Pitu gan (Henning)

C OXYTOCIC FACTOR (α-HYPOPHAMINE OXYTOCIN)

Hypophysin (Bayer)
Neo-Pituitarine (Opitura)
Physormon (Promonta)
Pitocin (Parke Davis)
Pituglandol (Roche)
Pituigan (Henning)
Pituigan forte (Henning)
Orasthin (Farben)

V – FOLLICULOIDS

I) FOLLICULOID HORMONES AND THEIR ESTERS ESTROGENIC HORMONES

a Estradiol

Estradiol (U S P XIII)
Aquadiol (National Drug)
Bar Estro (Barrington)
Bar-Estro-A (Barrington)
Dimenformon (Roche-Organon)
Estradiol (Brothers Pharm)
suspension (Maurry Veras)
Estrinol (Bellevue)
Estrogenic Hormone (Cabot)
Estrogenic suspension (Southern Med)
Estrovin (Bio-Intrasol)
Gynoestrol (Roussel Herman-Labor)
Macro-Pellets (Cabot)
Ovasterol (Frosst)
Ovestrin (Reed)
Ovocylin (Ciba)
Progynon-DH (Schering)
Progynon-Micropellets (Schering)
Estradiol + Estrogenic Substance
Estradiol suspension (Metropolitan)
Estrogenic substance (McNeil)
Femarrine (Endo)
Hormegen (Phys Drug)
Kurtestrin (Kurt)
Mikrogen (Durst)
Viestra (Vitamix)
Estradiol + Estrone
Compestrin (Harrower)
Endocreme (Hirestra Labs)
Estrogenic Hormone (Cole)
Estradiol trimethyl acetic acid ester (Lakeside)

b Estradiol Benzoate

Estradiol Benzoate (U S P XIII)
Benzhormovarine (Byla)
Difollisterol (Godeau)
Dimenformon Benzoate (Roche-Organon)
Fetofoliculina (Italian Drug)
Estradiol Benzoate (Horton & Converse)
Fenocyclin (Ciba)
Follikulin-Menformon (Degewop)
Oestroform (British Drug Houses)
Oestroglandol (Hoffman LaRoche)
Ovasterol B (Frosst)
Ovex (Lovens Kemiske Fabrik)
Ovocylin Benzoate (Ciba)
Perlatan (Boehringer)
Progynon B (Schering)
Unden (Farben)

c Estradiol Dipropionate

Dimenformon Dipropionate (Roche-Organon)
Diprovex (Byla)
Estradiol Dipropionate (Veras)
Ovocylin-Dipropionate (Ciba)
Progynon-DP (Schering)

d Ethynyl Estradiol

Ethynyl Estradiol (Under consideration for U S P XIV)
Estinyl (Schering)
Ertcylol (Ciba)
Lynoral (Roche-Organon)
Ronol (Horner)

e Estrone

Estrone (U S P XIII)
Estrone (Abbott Brothers Pharm Christina Lilly Medi-Synth Miller National Drug Warren-Teed)
Estrugenone (National)
Hiestrone (High)
Theelin (Parke Davis)
Thixol (Horton & Converse)
Estrone Aqueous
Aquacrine suspension (Endocrine)
Estrone suspension (Abbott Breon Christina Lilly)
Theelin suspension (Parke Davis)

f Estrone Sulfate

Conestron (Wyeth)
Linesterol (Lincoln Prop)
Oestrilin (Desbergers)
Premarin (Ayerst McKenna & Harrison)
Questrin Compound (Frosst)

g Estriol

Estriol (Abbott Lilly)
Theelol (Parke Davis)

h Estriol glucuronidate

Emmenin (Ayerst McKenna & Harrison)
Emmenoplex (Ayerst McKenna & Harrison)

i Estrogenic Substances (mixed)

Estrogenic Substances (Under consideration for U S P XIV)
Amniotin (Squibb)
Cartion s (Fougera)
Cavestragen (Cavendish)
Cyrestrone (Winthrop-Stearns)
Di-Folliculine Meurice (Union Chimique Belge)
Estras (Veras)
Estrinol (Bellevue)
Estrofol (Premo)
Estrogen-Miller (Miller)
Estrogenic Cartridges (Southern Med)
Estrogenic Hormone (Reed & Carnrick)

Estrogenic Substance (A P C, Ayerst McKenna & Harrison, Barry, Biorganic Labs, Boericke Runyon, [illegible] Pharm, [illegible] Direct [illegible] Drug, [illegible] Go- [illegible] Con- [illegible] Maltine [illegible] Miller, [illegible] Pyno- [illegible] Dohme, [illegible] Straub [illegible] Wilson Wyeth)
Estrogenol (Chemico)
Estrogyne (Estro)
Estro-Hart (Hart Drug)
Estrolin (Lakeside)
Estromone (Endo)
Estronat (National Drug)
Estropherol (Cabot)
Estroplex (Sonorol)
Estrotron (Pitman-Moore)
Estrovarin (Warren-Teed)
Estrovin (Bio-Intrasol)
Estrovite (Vitarine)
Estrugenone (Kremers-Urban)
Estrusol (C D Smith)
Femestrone (Kirk)
Folestrin (Armour)
Follacro (Schieffelin)
Follestrol (Blue Line)
Follicomone (Premo)
Follidrin (Astra)
Folliplex (Roland)
Follugen (Gotham)
Follumone (Endocrine)
Genestrolin (Christine)
Gynestrol (Penick)
Harvestrin (Harvey)
Hormestrin (Miller)
Hormobex (Lakeside)
Hormotone-T (Carnrick)
Hormovarine (Byla)
Kal-Estrin (Medi-Syrth)
Kestrone (Buffington)
Lentabs (Lederle)
Managen (Parke Davis)
Menestrin (Harris Prod)
Menformon (Roche-Organon)
Met-Estrin (Metropolitan)
Natestrin (Upjohn)
Neo-Amniotin (Squibb)
Novestrine (Gremy)
Ova-Estrin (Hospital Liquids)
Ovarian Substances (A P C Cole Flint Eaton Hildebrand Hynson Lafayette Marvell Purity Rorer Sharp & Dohme Sherman Smith-Dorsey, United Labs U S Standard Zemmer)
Ovestrin (Amer Parentrasol)
Ovestrinolin (Reed Pharm)
Ovhormone (Alpinol)
Ovifollin (Nyegaard)
Ovogen (Solex)
Plestrin (Harrower)
Prolagen (Drug Prod)
Proliculin (Merrell)
Semestrin (Massengill)
Thelestrin (Carnrick)
Tri-Estrin (Endocrine)
Urestrin (Upjohn)
Varium (Burroughs Wellcome)

2) ARTIFICIAL FOLLICULOIDS DIETHYLSTILBESTROL

(Δ3-3 4-di-(p-hydroxyphenyl)-hexane)

a Diethylstilbestrol (U S P XIII)
Des (Grant Chem)
Auren B (Farben)
Diestrene (Frosst)
Dietabs (Bever)
Diethrol (Merrell)
Diethylstilbestrol (Abbott, A B C Alpinol, Anglo-Canadian Armour Barlow-Maney Bates Bio-Intrasol Blue Line Boyle, Breon Bristol, Buffalo Buffington Burroughs Wellcome Carnrick, Chicago Pharm Ciba Cole Columbus Pharm Cowley Daniels Drug Prod Endo Ennes Estro Gold Leaf Harco Harrower Harvey, Hildebrand Horner Horton & Converse, Ingram, Intra Prod, Kremers-Urban Lakeside Lederle Lilly, Massengill Maurry McNeil, Merck, Merrell Miller, Penick, Pitman-Moore, Premo Purity, Rorer, Schieffelin, Seaver Sharp & Dohme Sherman, C D Smith, Smith-Dorsey Solex Squibb, Stearns Strasenburgh, Torigian Upjohn U S Standard Van Pelt & Brown, Veray, Warner, Warren-Teed Wendt Bristol, Winthrop Wyeth Zemmer)
Dioestrol (Frosst)
Distilbene (Borne)
Endestrol (Endocrine)
Estrobene (Ayerst McKenna & Harrison)
Estrol Cream (Estrol)
Estrosyn (Buffington)
Glo-Bestrol (Globe)
Metestrol (Metro)
Milestrol (Miller)
Neo-Oestranol (Crookes)
Sibol (Beebe Bristol Chicago Pharm, Daniels)
Stibilium (Desbergers)
Stilbestralp (Alpinol)
Stilbestrol (A P C, Dagra Phys Drug British Drug Houses)
Synthogen (National Drug)

b Benzestrol
(2 4-di(p-hydroxyphenyl)-3-ethyl hexane)
Benzestrol (Lederle, Schieffelin)
Cycloestrol (Bruneau)

c Dienestrol
(3 4-di-(p-hydroxyphenyl hexadiene-2 4), dehydrodiethylstilbestrol)
Cycladiene (Bruneau)
Dienesterol (Biophady, British Drug Houses Frosst, Ortho Rare White)
Novoestrol (Mees)

d Hexestrol
(3 4-di(p-hydroxyphenyl)-n hexane)
Dioestrol-DH (Frosst)
Hexesterol (British Drug Houses Cowley Direct Sales Horton & Converse Lanteen Massengill, Merrell Ortho Penick Prof Prod Rorer Vitamins Inc)

e Dimethyl Hexestrol Dipropionate
Meprane (Reed & Carnrick)

f Hexesterol + Phenobarbital
Hexesterol Phenobarbital (Buffalo Columbus Pharm, Lanteen Massengill Phys Drug)
Hexestrofen (Merrell)
Hexital (Ortho Prods)
Thelestrol (Carnrick)

g Diethylstilbestrol Monomethyl Ether
Monomestrol (Wallace & Tiernan)

h Diethylstilbestrol Dipalmitate
Stilpalmitate (Abbott)

i Diethylstilbestrol Dipropionate
Diethylstilbestrol Dipropionate (Blue Line Breon Burroughs Wellcome Lakeside Penick Winthrop)
Estrobene-DP (Ayerst McKenna & Harrison)
Stilbestronate (Blue Line)
Stilbestrol Dipropionate (Burroughs Wellcome)

VI — LUTEOIDS

1) PROGESTERONE AND CORPUS LUTEUM EXTRACTS

Progesterone (U S P XIII)
Corlutin (Pro Medico)
Corlutone (Gold Leaf)
Corpolutin (Astra)
Corpomone (Premo)
Corpus Luteum Ext (Abbott A P C Armour Bristol Cole Drug Prod Endo Haist Harrower Hosp Liquids Lafayette Lakeside Lilly Mallard Marvell Merrell National Drug Pitman-Moore Purity Rorer Sharp & Dohme Sherman Shores Smith Dorsey Stoddard Wilson Wyeth Zemmer)
Engestin (Harrower)
Gestormone (Godeau)
Glanestin (Ingram)
Homoflaveine (Byla)
Lipo-Lutin (Parke Davis)
Luteal (Istituto Opoterapico Nazionale)
Lutein Ext (Hynson Westcott & Dunning)
Luteocrin (Harrower)
Luteoglandol (Hoffman LaRoche Kretschmar)

Luteolin (Nyegaard)
Luteolinex (Kretschmar)
Luteosan (Kretschmar)
Luteotransannon (Kretschmar)
Luthorn (Upjohn)
Lutocycline (Ciba)
Lutocylin (Ciba)
Lutogestin (Solex)
Lutogyl (Roussel Herman-Labor)
Lutolin (Spanner)
Lutren (Larben)
Lutromone (Endo)
Lutrone (Buffington)
Nalutron (Winthrop)
Progesterol (Cabot C D Smith)
Progesterone (Abbott A B C, Alpinol, Armour Ayerst McKenna & Harrison Bellevue, Biorganic, Bishop Boyle Breon Cabot, Carnrick Chemico, Chicago Pharm Cowley, Dalrone Denver Mud Direct Sales Drug Prod Empire Endocrine Ennes Pharm, Estro Fitch Flint Eaton, Forbes, Frosst, Glidden Gotham Harrower Hart Drug Hema, Horton & Converse, Intra Prod, Kings County Kremers Urban Lakeside Leader Lederle Lilly Loyal Massengill Maurry, McNeil, Medi-Synth Metropolitan Miller Morris, Parentrasol Phys Drug Prof Prod, Reed & Carnrick, Schieffelin Sherman Squibb, Torigian United Labs Upjohn Warren-Teed)
Progestilin (Desbergers)
Progestin (Abbott Barrington, Bio-Intrasol Buffington, Drug Prod Flint Eaton, Gotham Harrower Hospital Liquids Kirk Lakeside Lilly Medi-Synth National Purity, Pynosol Roche Organon Smith Dorsey, U S Standard Yale)
Progestine (N V Organon-Oss)
Progestone (Carnrick)
Progestron (Pitman Moore)
Progitas (Verax)
Progonasyl (Progonasyl)
Proluton (Schering)

2) PREGNENINOLONE

Anhydrohydroxy-progesterone (U S P XIII)
Lutocylol (Ciba)
Pranone (Schering)
Progestoral (Roche-Organon)
Progestin (Frosst)

3) ETHYNYL-ANDROSTENEDIOL

Sabarol (Horner)

4) PROGESTERONE + ESTRADIOL BENZOATE

Di-Pro (Roche-Organon)
Progestradiol (Ciba)
Prometron (Schering)

5) PROGESTERONE + ESTROGENIC SUBSTANCE

Ceclogesterin (Upjohn)
Estrogen & Progesterone (Breon Empire Smith Dorsey)
Estrone-Progesterone (Miller)
Estroplex (Sororol)
Estrotate (Lakeside)
Femestro-Lutin (Kirk)
Procyclo (Metropolitan)
Proculin (Cabot)
Pro-Estrin (Vitamix)
Progenol (Metropolitan)
Promegen (Phys Drug)

VII — a INSULIN REGULAR CRYSTALLINE OR NON-CRYSTALLINE

Insulin Injection (U S P XIII)
Iletin (Lilly)
Insulin (Bayer Connaught Degewop Mack Mulford Searle Sharp & Dohme Squibb, Ulm)

b INSULIN MODIFIED

Protamin Zinc Insulin Inj (U S P XIII)
Globin Insulin with Zinc (Burroughs Wellcome Squibb)
Globin Insulin (Lilly)
Protamin Zinc Iletin (Lilly)
Protamin Zinc Insulin (Sharp & Dohme Squibb)
Zinc Iletin Crys (Lilly Sharp & Dohme)
Zinc Insulin Crys (Squibb)

VIII — PARATHYROID HORMONE

Parathyroid Injection (U S P XIII)
Hytakerol (Winthrop)
Parathyroid Ext (Armour Lilly Wilson)
Parathyroid Gland (Burroughs Wellcome)
Parathyroid Hormone (A P C Armour Lilly Parke Davis, Squibb, United Labs Wilson)
Paroidin (Parke Davis)

IX — TESTOIDS (MALE SEX HORMONES ANDROGENS)

A CRYSTALLINE TESTOSTERONE AND ITS DERIVATIVES

a Testosterone

Aceto-Sterandryl (Roussel Herman Labor)
Hormogen C (Mallard)
Male Sex Hormone (Hoosier Pharm)
Oreton F (Schering)
Perandrone (Ciba)
Testin (Nyegaard)
Testodrin (Astra)
Testosterone "Lingusorbs" (Ayerst McKenna & Harrison)
Testosterone (Biorganic Cabot, Chicago Pharm Duffield Estro, Gotham Loyal Morris, Phys Drug Vitamix)

b Methyl testosterone

Methyl-testosterone (U S P XIII)
Glosso-Sterandryl (Roussel)
Metandren (Ciba)
Metosterone (Ayerst McKenna & Harrison)
Methyl-Testosterone (Armour Parke Davis Phys Drug Rare Upjohn, Southern Med Vitamix)
Neo-Hombreol M (Roche-Organon)
Orchisterone-M (Frosst)
Oreton-M (Schering)

c Testosterone propionate

Testosterone propionate (U S P XIII)
Androtestone (Godeau)
Lydin (Harrower)
Orchisterone-P (Frosst)
Neo-Hombreol P (Roche-Organon)
Oreton (Schering)
Perandren (Ciba)
Testhormone (Alpinol)
Testosterone propionate (Armour Chicago Pharm Denver Mud Direct Sales, Estro Gotham Parke Davis Phys Drug Rare, Vitamix)
Testodrin (Astra)
Testostinate (Cabot)
Virosterone (Endo)

d Testosterone Aqueous

Aqueous Testrone (Miller)
Malogen (Testagar)
Testacrine (Columbus)
Testosterone suspension (Endo)

B TESTICULAR EXTRACTS

Androgenic Hormone (Chicago Pharm Pynosol)
Androgenol (Chemico Lab)
Androplex (Christina)
Androstin (Ciba)
Androsol (Smith)
Cavolestrone (Cavendish)
Glandular Comp Male (Carnrick)
Gleydig (Schieffelin)
Homovir (Anglo-French)
Luporein (Stoddard)
Male Sex Hormone (Bellevue)
Malestrone (Kirk)
Natural Orchic (Miller)
Orchiben (Marvell)
Orchic Concentrate (Drug Prod U S Standard)
Orchic Extract (Lafayette, Lakeside National Drug Wilson)
Orchic Liquid (Endo)
Orchic-ol (Cole)
Orchic Solution (Harrower)
Orchic Substance Desic (Abbott Armour Cavendish, Lilly Parke Davis Sherman Wilson, Zemmer)
Testacoids (Reed & Carnrick)
Testicular Ext (Estro, Fitch Leroy)
Testicular Hor Bylaxa Amp (Fougera)
Testiforten (Kretschmar)
Testigen (Solex)
Testiglandol (Kretschmar)
Testilax (Verax)
Testilon (Oxford)
Testosterone (Bartos)
Testostrin Amp (Pro-Medico)
Virone (Gold Leaf Pharm)

X — THYROID HORMONE

A THYROID EXTRACT

Thyroid (17-23% Iodine) (U S P XIII)
Desi-Thyroid (Frosst)
Elytractin (Boyer)
Endothyrin (Harrower)
Glythoid Pills (Schieffelin)
Ityphen (Straus)
Proloid (Maltine)
Thyentabs (Carnrick)
Thyracoids (Reed & Carnrick)
Thyractin (Winthrop)
Thyranon (Roche-Organon)
Thyrobrom (Van Patten)
Thyroid (Abbott, A B C A P C, Armour, Artaco Bates Bellevue Biorganic Bishop, Blue Line, Boyle Breon Bristol Buffalo Buffington Burroughs Wellcome, Carnrick, Cheplin Chicago Pharm Clinic Line Daniels Drug Prod, Endo, Endocrine Harco Harrower, Harvey Hildebrand, Horton & Converse Hynson Westcott & Dunning, Jamieson Kremers-Urban Kretschmar Lakeside, Lederle Lilly Massengill Maurry McNeil Merrell Metro Miller National Drug Park Drugs Parke Davis, Petroline, Pitman-Moore Premo, Prof Prod, Purity, Rorer, Schering Schieffelin, Seal, Seaver Sharp & Dohme, Sherman, Smith-Dorsey Solex, Squibb Stayner, Stoddard, Success, Supreme Testagar, United Labs, Upjohn, Van Pelt & Browne Viobin, Warren-Teed Wendt Bristol Wilson, Wyeth)
Thyrowdal (C D Smith)
Thyronal (Desbergers)
Thyroprotein (Parke Davis)

B THYROXIN (64% Iodine)

Thyroxin (U S P XIII)
Thyroxine (British Drug Houses, Roche-Organon, Roche-Schering-Henning, Squibb)
Thyroxin Fraction (Squibb)

C DI-IODO-TYROSINE

Di-Iodo-Tyrosine (Roche-Organon)
Flitycan (Farben)
Thyreoidin (Merck)
Thyreoglandol (Henning-LaRoche)
Thyrowop (Degewop)

THE HISTORY OF ENDOCRINOLOGY

A good deal can be learned from the manner in which endocrinologic discoveries were made in the past, since problems similar to those which have already been solved present themselves to us now and will probably arise again in the future In choosing our problems and in preparing our plans for medical research, it is useful to profit by the experience of our predecessors History can teach us to recognize promising and important subjects at an early date, by revealing the form under which such problems appeared, much before their implications were fully understood and proven

This brings us to the most fundamental question an investigator must consider. what is an important research problem? I believe that experimental medicine is not an abstract, but an applied science Admittedly, in the early stages, it is often difficult to foretell whether a problem will have important applications to practical medicine, but at least we should select our problems keeping in mind that practical applicability is their most noble goal Medical research undertaken merely as a sophisticated type of mental gymnastics — a viewpoint often defended by the slogan 'science for science's own sake' — appears unworthy of the traditions of the medical profession, whose primary aim has always been, and should remain, to help the sick

In choosing a topic for medical research I have found it useful to be guided by the adage *"The most important problem is that which means most to most people"* Applying this dictum to endocrinology, the best problems for investigation would be those most likely, directly or indirectly, to help in the therapy of the most common and serious diseases It must not be disregarded, however, that investigations which lend themselves particularly well to generalizations and the formulation of laws applicable to a large number of endocrine processes, are also of great import in accordance with our maxim. Even tentative generalizations help to formulate hypotheses and theories which preliminarily connect a number of apparently unrelated and inexplicable facts The history of endocrinology clearly shows that the *horror of interpretative thought* — which developed as a reaction against the purely speculative, dialectic approach to medicine prevalent in past centuries — is unjustified It is always advantageous to connect cognate facts through a preliminary hypothesis Interrelations — so important in endocrinology — can only be elucidated after we have sketched a temporary plan which coordinates the known facts as well as it is possible on the basis of the knowledge available at the time The history of endocrinology has clearly demonstrated, furthermore, that even incorrect theories are often of great help in unveiling the secrets of nature, as long as we regard them merely as concrete formulations of possibilities, which, by virtue of their concreteness, lend themselves to be proven or disproven by subsequent observation The hypothetical nature of such theories, or of any link in a chain of theoretic interrelations, must always be clearly emphasized, however, and the investigator must be prepared to change his theories without any feeling of remorse or resentment, as soon as new facts require a modification The hazy outlines of indistinct concepts become sharp when they crystallize into a definite theory, and it is only then that we can subject their correctness to experimental proof

It is an unfortunate fad among many contemporary scientists to limit publications to the mere registration of observations, spurn-

ing their interpretation as vain verbiage. It must be pointed out that the listing of facts is not science. By definition, science is "accumulated knowledge systematized and formulated with reference to the discovery of general truths or the operation of general laws" (Webster's Dictionary). The mere enumeration of facts is undoubtedly the "safest" procedure but an author who chooses this technic for the publication of his results must realize that he contributes nothing to science until a bolder colleague attempts their evaluation at the risk of being blamed for a possible error.

If, for a moment, I may abuse of my priviledged position as an author who has no editor to put him in his place, I would also like to mention that most of the pleasure which the investigator derives from his work lies in the "artistic" interpretation of his observations In music, for instance, single tones have no artistic value, melodies result only if tones are connected in a certain order; the more sophisticated musician will even want to harmonize the melody by supporting notes and several independent melodies must be coördinated to create counterpoint Very much the same can be said about the various degrees of refinement in the artistic enjoyment and evaluation of scientific discoveries If we substitute facts for notes and coördination of several facts in the theoretic connection of a "chain of events" for melodies, then the elucidation of independent factors influencing any one link in the chain of events would correspond to chords To create counterpoint we have to integrate several independent chains of events which, at certain points, cooperate for the good of the organism (Note to students: please forgive this, I promise you will not be "held responsible" for it at examination time!)

Endocrinology as we know it to-day is a young science hardly more than fifty years of age It would be difficult, however, to determine exactly when and where the thought has originated that there is an integration of organs through humoral means

In an historic survey it is almost inevitable that great discoveries are connected with the names of certain individuals We must realize, however, that the historian of wars, as that of peaceful endeavors selects most of his "heroes" more or less arbitrarily. When we review the story of an accomplishment it is almost impossible to determine in retrospect exactly what *the hero's exploits were*, and to what extent the work of those whose names are pointed out to posterity were dependent upon the accomplishments of the many "unknown soldiers" who went before them

Some harmonious and lawful coöperation, between the different organs of the body, has been suspected since times immemorial and was designated as the "consensus partium"

It has long been anticipated furthermore that certain organs contain substances (or "spirits" or "potentialities") which exert beneficial actions when introduced into the body. It is on the basis of such indistinct concepts that in ancient medicine, the organs of animals, or even of enemies killed in battle, have been ingested in order to give strength and courage or to cure diseases. One of the oldest medical texts, the Egyptian *Papyrus of Eber*, enumerates many organ extracts among the 700 drugs which it discusses. Such ORGANOTHERAPY has also been advocated by the Greek philosopher *Aristotle* (384-322 B.C.), and the Roman *Pliny the Elder* (23-79 A.D.) devoted all of books XXVIII-XXXII of his Natural History to "Materia Medica," an enumeration of medicines derived from the bodies of men and animals.

Paracelsus (1493-1541) (his true name was Theophrastus Bombastus von Hohenheim) a Swiss physician, often described as the father of pharmaceutic chemistry, was apparently the first, however, to justify such practices by a scientific hypothesis, characterized by his slogan "Similia similibus curantur," according to which a diseased organ is best cured by administration of a similar organ. Thus, we arrive at a fairly clear formulation of SUBSTITUTION THERAPY.

The therapeutic administration of animal organs, and organ extracts, constantly gained in popularity. According to *Winkler*, the pharmacies of Innsbruck (Austria) still carried 122 official preparations of this type, as late as 1765. Even human organ extracts, such as "Cranium humanum preparatum" or "Oleum cranii humani" were prepared from the bodies of executed men and distributed through the pharmacies.

X — THYROID HORMONE

A THYROID EXTRACT

Thyroid (17-23% iodine) (U S P XIII)
Desi-Thyroid (Frosst)
Elyractin (Boyer)
Endothyrin (Harrower)
Glythoid Pills (Schieffelin)
Ityphen (Straus)
Proloid (Maltine)
Thyentabs (Carnrick)
Thyracoids (Reed & Carnrick)
Thyractin (Winthrop)
Thyranon (Roche-Organon)
Thyrobrom (Van Patten)
Thyroid (Abbott, A B C A P C., Armour Artaco, Bates, Bellevue Biorganic, Bishop, Blue Line, Boyle Breon Bristol Buffalo, Buffington Burroughs Wellcome, Carnrick, Cheplin Chicago Pharm Clinic Line Daniels Drug Prod Endo, Endocrine Harco Harrower, Harvey Hildebrand Horton & Converse Hynson Westcott & Dunning Jamieson Kremers-Urban Kretschmar Lakeside, Lederle, Lilly Massengill Maurry, McNeil Merrell, Metro, Miller, National Drug Park Drugs Parke Davis Petroline, Pitman-Moore Premo Prof Prod Purity, Rorer Schering Schieffelin, Seal Seaver Sharp & Dohme, Sherman, Smith-Dorsey, Solex Squibb Stayner Stoddard Success, Supreme Testagar, United Labs Upjohn, Van Pelt & Browne, Viobin, Warren-Teed Wendt Bristol, Wilson, Wyeth)
Thyroidal (C D. Smith)
Thyronal (Desbergers)
Thyroprotein (Parke Davis)

B THYROXIN (64% Iodine)

Thyroxin (U S P. XIII)
Thyroxine (British Drug Houses Roche Organon, Roche-Schering-Henning Squibb)
Thyroxin Fraction (Squibb)

C DI-IODO-TYROSINE

Di-Iodo-Tyrosine (Roche-Organon)
Fluigran (Farben)
Thyreoidin (Merck)
Thyreoglandol (Henning-LaRoche)
Thyrowop (Degewop)

THE HISTORY OF ENDOCRINOLOGY

A good deal can be learned from the manner in which endocrinologic discoveries were made in the past, since problems similar to those which have already been solved present themselves to us now and will probably arise again in the future In choosing our problems and in preparing our plans for medical research, it is useful to profit by the experience of our predecessors History can teach us to recognize promising and important subjects at an early date, by revealing the form under which such problems appeared, much before their implications were fully understood and proven.

This brings us to the most fundamental question an investigator must consider what is an important research problem? I believe that experimental medicine is not an abstract, but an applied science Admittedly, in the early stages, it is often difficult to foretell whether a problem will have important applications to practical medicine, but at least we should select our problems keeping in mind that practical applicability is their most noble goal Medical research undertaken merely as a sophisticated type of mental gymnastics — a viewpoint often defended by the slogan 'science for science's own sake' — appears unworthy of the traditions of the medical profession, whose primary aim has always been, and should remain, to help the sick

In choosing a topic for medical research I have found it useful to be guided by the adage *"The most important problem is that which means most to most people"* Applying this dictum to endocrinology, the best problems for investigation would be those most likely, directly or indirectly, to help in the therapy of the most common and serious diseases It must not be disregarded, however, that investigations which lend themselves particularly well to generalizations and the formulation of laws applicable to a large number of endocrine processes, are also of great import in accordance with our maxim. Even tentative generalizations help to formulate hypotheses and theories which preliminarily connect a number of apparently unrelated and inexplicable facts. The history of endocrinology clearly shows that the *horror of interpretative thought* — which developed as a reaction against the purely speculative, dialectic approach to medicine prevalent in past centuries — is unjustified It is always advantageous to connect cognate facts through a preliminary hypothesis Interrelations — so important in endocrinology — can only be elucidated after we have sketched a temporary plan which coordinates the known facts as well as it is possible on the basis of the knowledge available at the time The history of endocrinology has clearly demonstrated, furthermore, that even incorrect theories are often of great help in unveiling the secrets of nature, as long as we regard them merely as concrete formulations of possibilities, which, by virtue of their concreteness, lend themselves to be proven or disproven by subsequent observation The hypothetical nature of such theories, or of any link in a chain of theoretic interrelations, must always be clearly emphasized however, and the investigator must be prepared to change his theories without any feeling of remorse or resentment, as soon as new facts require a modification The hazy outlines of indistinct concepts become sharp when they crystallize into a definite theory, and it is only then that we can subject their correctness to experimental proof

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must credit Bernard, not only for clearly formulating the concept of endocrine activity, and for creating the now current term "internal secretion," but also for having first expressed one of the most fundamental physiologic laws that of the importance of maintaining the normal composition of the "*milieu intérieur*," the body humors

He failed to differentiate, however, between actual hormone production, as we now understand it, and the discharge into the blood of metabolites, nutrients or even the blood cells themselves Among the purely endocrine glands, he listed the adrenal, the thyroid, the spleen, thymus and lymph nodes, among the partially-endocrine organs, the liver, which secretes glucose into the blood, and the lungs, which oxygenate it.

The actual birthday of endocrinology is traditionally listed as June 1st, 1859, when the distinguished French physician *Brown-Séquard*, then 72 years old, made his now historic communication to the Société de Biologie de Paris He reported a truly astonishing degree of rejuvenation after having treated himself with subcutaneous injections of a Pasteur-filtered, aqueous, dog-testis suspension However, on the basis of what we now know about the chemical properties of testis hormone, his extracts could not possibly have contained a sufficient amount to produce any detectable effect Testosterone, the hormone in question, is comparatively insoluble in water and its concentration in the testis is so low that an adequate dosage could never be injected in the form of a crude suspension. Nevertheless, the venerable old gentleman described the process of his alleged rejuvenation, in its most intimate details, with so much satisfaction and contagious enthusiasm that the medical world began to take an active interest in the possibilities of endocrinology. It must be admitted, furthermore, that he so clearly outlined the scope of the endocrines as an independent integration-mechanism separate from the nervous system, that he gave that final impetus to medical thinking along these lines which was necessary to establish endocrinology as a science He said: ' Nous admettons que chaque tissu et plus généralement, chaque cellule de l'organisme, sécrète pour son propre compte, des produits ou des ferments spéciaux, qui sont versés dans le sang et qui viennent influencer, par l'intermediaire de ce liquide, toutes les autres cellules rendues ainsi solidaires les unes des autres par un mécanisme autre que le sys'ème nerveux "

It is especially noteworthy that at the time of Brown-Sequard s famous lecture, the meticulous observations and the well-founded deductions of Claude Bernard were already known, as were the deductions of anatomists and histologists who postulated an internal secretion on the basis of morphologic evidence. We might add that in England *Thomas Addison* (1855) had already described the disease which now bears his name, *Hilton-Fagge* (1871) spoke of sporadic cretinism due to absence of the thyroid and *W.-W. Gull* (1873) pictured spontaneous myxedema in adults, the brothers *Reverdin* (1879) in Switzerland noted 'post-operative myxedema" following thyroidectomy for goiter — Any one of these earlier discoveries could have been the cradle of endocrinology, but it is an historic fact that they were not. Apparently the strictly endocrinologic implications of these discoveries were not described with sufficient poignancy to interest the medical profession in the basic concepts of endocrinology. It is somewhat humiliating to note that our science began with an error due to subjective interpretation of observations and no one will condone Brown-Séquard s lack of objectivity Yet, there is a lesson to be learned from his paper by those so fearful of 'over-dramatizing" their observations that they write drab and monotonous papers, "catalogues of facts' without an effort of synthetic interpretation and evaluation.

These are the salient historic events in the evolution of the concept of internal secretion Additional data concerning individual glands will be found in the 'Historic Introduction' to the corresponding sections

REFERENCES

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A textbook (353 pages, numerous figures, charts and tables, no references) mainly written for the practising endocrinologist. (In French.)

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At this time, we are still very far from the true understanding of ENDOCRINE ACTIVITY AS A PHYSIOLOGIC PROCESS WHICH HELPS TO CORRELATE the parts of the body. The integration of the activities of distant organs has chiefly been considered as a function of the nervous system ever since the French philosopher *Descartes*, in the 17th century, and later the Viennese physiologist *Prochaska* (1784) developed the concept of nervous reflexes as the "reflexion of sensory into motor impulses."

New possibilities of integration were raised through the discovery by the English physician *Harvey* (1628) of the blood circulation.

In his treatise "Analyse Médicinale du Sang" (1775), *Théophile de Bordeu* of Montpellier, expressed the view that every organ produces specific substances which enter into the blood and that these are useful to the organism. He also suspected that deficiency symptoms after castration might be due to a failure of humoral substances produced by the sex glands. He expressed his premonition, furthermore, that ANOMALIES IN HUMORAL SECRETIONS PLAY AN IMPORTANT RÔLE IN PATHOLOGY by saying that "C'est au médecin à suivre et à classer les divers reflux qui surviennent par la faute de chaque organe en particulier." (It is up to physicians to follow and classify the divers ebbs which supervene due to failure of each particular organ).

FROM A PURELY MORPHOLOGIC VIEWPOINT, most glands of internal secretions have been known for a very long time. Only a few have been discovered comparatively recently, e g., the adrenals, by *Eustachius* (1563) in his treatise "de Glandulis Quae Renibus Incumbunt," and the parathyroids by *Sandstrom* (1879). It was not clearly understood, however, that these organs are specialized for the production of internal secretions.

In his textbook of physiology (1844) the German physiologist, *Johannes Muller* described as "ganglia sanguineo-vasculosa" the thyroid, the adrenals, the spleen and the placenta. He states that these ductless glands: "exert a plastic influence upon the humors which circulate through them and return from them to the general circulation; they have no relations with the exterior, as have the other glands."

However, all the evidence cited above was based either upon mere speculation, or only upon the interpretation of the morphologic structure of endocrine glands. *John Hunter* in England, probably around 1771, and *A. A. Berthold*, (Germany) in 1849, were apparently the first to demonstrate EXPERIMENTALLY that the virilizing effect of the testis is actually due to an endocrine activity. They found that castrated cocks retained their normal male appearance, libido, fighting instincts, comb and wattles — that is, they remained masculine — if the testes were re-implanted into a different part of the body. From this, Berthold concluded that the "consensus" in question is due to the influence of the testes upon the blood, which, then, in its turn, influences the organism in general. It is noteworthy that the first proof for an "internal secretion" was furnished by the elimination of all other possibilities. All other connections of the transplanted testes (nerves, ducts, etc.) having been severed, the glands could act only by influencing the blood brought to them by the invading vessels.

These early observations were forgotten because a few subsequent investigators failed to confirm them The theory of an internal secretion did not receive general attention until the great French physiologist, *Claude Bernard* (1813-78) first clearly expressed the thought that in addition to the 'secretions externes' of the ordinary glands, all organs produce a "secrétion interne' through which they influence the "milieu intérieur" whose composition they help to maintain invariable (1857) Hence, we

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Merely of historic interest.

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A book (770 pages) listing those drugs (including hormones) which the Council on Pharmacy and Chemistry has found acceptable. In general, standard drugs described in the United States Pharmacopeia are not included, so that this volume (known as N. N. R.) complements the latter. The book also contains a description of various bioassay methods, units, and details for the preparation of recommended hormone products.

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A treatise (985 pages, 158 figures, numerous tables and references) containing very authoritative sections concerning the rôle of the hormones upon metabolism and its diseases. The chapters on diabetes mellitus, diabetes insipidus, hyperinsulinism, obesity, as well as those on carbohydrate, protein, lipid, mineral and water metabolism are particularly instructive for the endocrinologist.

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An extensive treatise (1912 pages, 933 illustrations, numerous references) in three volumes and an index volume. The book contains an enormous amount of information such as anthropologic measurements as influenced by age or endocrinotrophies, numerous case reports, etc., although the theoretic interpretations are often very subjective, it is still of more than historic interest.

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An outline (126 pages, numerous illustrations, 65 references) of endocrinology, mainly based on highly simplified, but amusing charts and cartoons.

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An excellent textbook (644 pages, 132 illustrations and a selection of key references) highly recommendable to medical students and physicians.

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An authoritative textbook (571 pages, 157 figures, numerous references) primarily devoted to endocrine problems in gynecology, it also contains a clear and concise summary of other aspects of endocrinology.

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The first volume (886 pages, numerous tables and references, few figures) is a series of excellent papers by highly competent specialists, but without any attempt to correlate the chapters into an integrated synopsis The chapters on hormones in plants and invertebrates (195 pages) probably represent the best synopsis of this field now available Clinical problems are not discussed although they will receive a limited amount of space in the second volume, which is now in preparation

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A textbook (415 pages, 26 figures, few references) concerning technics and methods of endocrinology Mainly based on the author's own experience (In German)

RIDDLE, O *Endocrines and Constitution,* in Doves and Pigeons Carnegie Institution of Washington Publication 572, Washington (1947)

Summary (306 pages 7 illustrations, many charts and tables, numerous references) of the author's extensive personal investigations concerning the influence of race, sex and genetic constitution upon the development of endocrines in certain birds Recommended only for specialists

ROLLESTON, H D *The endocrine organs in health and disease with an historical review.* Oxford University Press, Publ., Oxford, (1936)

A textbook (521 pages, numerous references) mainly devoted to clinical problems in endocrinology. 35 of the 45 figures depict prominent endocrinologists, most of whom exhibit no overt endocrinopathy. The book is now somewhat outdated, but especially the historic sections still provide interesting and instructive reading

ROWE, A. W.: *The differential diagnosis of endocrine disorders.* London (1933).

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A textbook (912 pages, 216 figures, no references) which contains an extraordinarily large number of data, but places almost equal emphasis upon doubtful and fully established observations, hence it is most useful to those having sufficient experience to evaluate the data for themselves. (In French)

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An astonishing opus (539 pages, 30 figures, 324 references) in which the author comes to the conclusion that "by restoring the balance of the pituitary gland, tumour growth is arrested and the patient saved".

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An encyclopedic treatise planned eventually to cover the whole field of endocrinology Section I (in 4 volumes) The Steroids (728 pages, formulae and synoptic charts) deals with the chemistry and pharmacology of the steroids Of section IV (The Ovary) only the Ovarian Tumors (in 2 volumes) have been completed (876 pages, numerous illustrations and more than 15000 references) The individual parts are self-contained monographs independent of the other sections which have not yet been published The encyclopedia is edited in loose-leaf form and intended to act as a critical guide to the entire endocrine literature Additional pages will be printed in order to keep the work up-to-date

SEVRINGHAUS, E L: Endocrinology in The *1945 year book of neurology, psychiatry and endocrinology* The Year Book Publishers, Chicago (1946)

An outline (332 pages, 31 figures, few references) summarizing the most important recent advances in clinical endocrinology; partly based upon case reports

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A brief outline (144 pages, no illustrations or references) of endocrine diagnosis, mainly in the form of synoptic charts

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An extensive treatise (1742 pages, 319 figures and charts, numerous references) principally concerned with clinical problems (In Spanish)

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An encyclopedia (5714 pages, 1105 illustrations, numerous references) in five large volumes which treats both the theoretic and clinical aspect of endocrinology The various chapters are written by different authors and are of very variable quality. Unfortunately, many of the references are incomplete, so that the book does not serve as a good guide to the literature

HOSKINS, R G. *Endocrinology, the glands and their functions* W W Norton & Company, Inc Publ, New York (1941)

An amusingly written outline (388 pages, few illustrations and references) of endocrinology which may serve as an introduction to this subject

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A textbook of physiology (1343 pages, 497 figures, 82 tables, numerous references) containing a particularly instructive summary of endocrinology (In Spanish)

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An excellent textbook (485 pages, few illustrations and references) compiled by leading Dutch endocrinologists (In Dutch)

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A textbook of experimental endocrinology (513 pages, 142 figures, numerous references) which is now merely of historic interest.

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A brief outline (152 pages, 7 illustrations, key references) concerning the pharmacology of the hormones German trade preparations are considered almost exclusively (In German)

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A voluminous textbook (883 pages, 194 figures, 37 charts and tables, few references) describing the diseases of the endocrines mainly on the basis of the author's own experience

LUTZ, W., H. W. SIEMENS AND J. STRANDBERG *Vererbung innere Sekretion Stoffwechsel* J Jadassohn's Handbuch der Haut- und Geschlechtskrankheiten *3,* (1929) Verl. von Julius Springer, Berlin (1929)

A monograph (389 pages, 57 figures numerous references) which deals mainly with the rôle of hormones in dermatology (In German)

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A brief booklet (222 pages, 8 plates, 22 figures, key references) principally concerned with problems of clinical diagnosis and therapy

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The proceedings (243 pages, numerous illustrations and 1200 references) of a research conference It is a most instructive up-to-date summary, concerning the chemistry of the hormones, compiled by 17 leading authorities in this field

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A textbook of endocrinology (467 pages, 17 figures, no references) which is now merely of historic interest (In French)

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SEVRINGHAUS, E L : Endocrine Therapy in *General Practice* The Year Book Publishers, Inc, Publ, Chicago (1942).

A small outline of clinical endocrinology (243 pages, 47 illustrations, no references) mainly intended for the practitioner.

SÉZARY, A. AND M LABBÉ (ED): *Glandes endocrines Maladie de la Nutrition* (By various authors). In A Laffont and F Durieux's *Encyclopédie médico-chirurgicale* Masson et Cie Publ, Paris (1935)

A voluminous loose-leaf tome concerned primarily with the clinical problems of endocrinology It will constantly be brought up-to-date by the addition of new looseleaf sheets (In French)

SÉZARY, A, et J. LENÈGRE *Précis de Pathologie Médicale* Tome VIII Maladies Endocriniennes Masson et Cie, Publ, Paris (1948).

A textbook (714 pages, 155 figures, no references) dealing mainly with clinical problems of endocrinology (In French)

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Merely of historic interest.

STOCKARD, C. R *The genetic and endocrinic basis for differences in form and behavior.* Wistar Institute of Anatomy and Biology, Publ., Philadelphia (1941)

A classic treatise (775 pages, 128 figures, 113 plates, numerous tables and references) concerning the rôle of heredity in endocrinology.

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Merely of historic interest.

TURNER, C D *General Endocrinology* W B Saunders Co, Publ, Philadelphia (1948)

An excellent textbook (604 pages, 164 charts and figures, 1367 references) written mainly from the zoologist's point of view The section on endocrines in invertebrates (73 pages), and several other often neglected fields of theoretical endocrinology, are especially well written, but clinical problems are given little prominence (e g, myxedema, 1 page, diabetes mellitus, 2 pages).

TWOMBLY, G H and G T PACK (ED) *Endocrinology of Neoplastic Diseases* A Symposium by Eighteen Authors Oxford University Press Publ, New York (1947).

A symposium (392 pages, numerous charts and figures, many references) on the relationship between hormones and neoplastic disease It represents a good summary of this field, but is slightly outdated

UNITED STATES PHARMACOPOEIAL CONVENTION *The Pharmacopoeia of the United States of America* Twelfth Revision Board of Trustees, Publ., Mack Printing Company, Easton (1942).

This book (880 pages, numerous tables) as well as the British Pharmacopoeia, represent authoritative manuals describing the characteristics of those drugs (including hormones) whose utility is most definitely established. It also contains sections on: reference standards, international standards, patented and trade-mark products and regulations governing the manufacture and sale of drugs.

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An extensive treatise of medicine (few figures and references) by prominent French clinicians, in which two sections are devoted to diabetes (60 pages) and other endocrine problems (128 pages) respectively. (In French)

VIÉGAS, A. PINTO *Endocrinologia Clinica* Livraria Editora Paulo Bluhm, Belo Horizonte, 1941

A textbook (292 pages, 53 illustrations, few references) mainly intended as a guide for the clinical endocrinologist (In Portuguese.)

VINCENT, S *Internal secretions and the hormonal glands,* 3rd Ed, Edward Arnold & Co, Publ., London (1924).

Merely of historic interest.

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A textbook (923 pages, 327 illustrations, numerous references) of clinical endocrinology primarily for the practicing physician

WOLF, W *Endocrinology in modern practice.* 2nd Ed (1939)

A voluminous textbook primarily intended for practitioners

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A textbook of internal medicine (1204 pages, 275 figures, numerous tables and references) in which the diseases of the endocrines and of metabolism are particularly clearly described

ZONDEK, H *The diseases of the endocrine glands.* 4th Ed Edward Arnold & Co Publ, London (1944).

A textbook (496 pages, 180 figures, numerous references) in which rather prominent emphasis is placed upon inadequately investigated subjects and upon the author's personal observations

SPECIAL ENDOCRINOLOGY

I

THE STEROIDS

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INTRODUCTION

A special section of this book is devoted to a general discussion of the steroids because of the close chemical, physiologic, pharmacologic and metabolic relationships which exist between the individual members of this group.

The chemical and pharmacologic terminology of the steroids; the classification of the compounds themselves and of their actions; the interrelations between the chemical structure and the pharmacologic activity of steroids are all subjects which best lend themselves to synoptic discussion

It will also be kept in mind that the same steroid hormone may be elaborated by several endocrines (e g . gonads, adrenal cortex and placenta) hence, many steroids, as well as their metabolites, cannot be regarded as the specific products of any one endocrine gland Furthermore, the overlap between the pharmacologic actions of chemically different steroids is so considerable that it appears best to devote a separate section to the interrelations which exist between the members of this group

In the sections dealing with the individual, steroid-producing endocrine glands, namely the Ovary, Testis, Adrenals and Placenta (see Pregnancy), the reader will find additional data concerning those steroid hormones which are particularly characteristic of the activity of any one of these organs.

In the present section we wish to deal mainly with the following subjects :

(1) Occurrence and rôle of the steroids in nature

(2) Chemical terminology and classification of the steroids

(3) Pharmacologic terminology and classification of the steroids.

(4) Interrelations between the various pharmacologic properties of the steroids (pharmaco-pharmacologic *interrelations*).

(5) Interrelations between the pharmacologic properties and the chemical structure of the steroids (pharmaco-chemical interrelations).

(6) Biogenesis and metabolism of the *steroids*

OCCURRENCE AND RÔLE OF THE STEROIDS IN NATURE

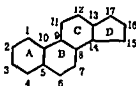
The steroids are derivatives of the hydrocarbon cyclopentanoperhydrophenanthrene, sometimes also referred to as norestrane (see below). Derivatives of this basic four ring compound are very widely distributed in nature and many of them are characterized by outstanding physiologic and pharmacologic effects

THE NATURALLY OCCURRING GROUPS OF THE STEROIDS *are* :

(1) Animal sterols (Zoosterols).
(2) Plant sterols (phytosterols).
(3) Bile acids.
(4) Steroid hormones.
(5) Odoriferous steroids
(6) Cardiac aglucones
(7) Sapogenins (e g . Digitalis sapogenins).
(8) Genins of the toad venoms.

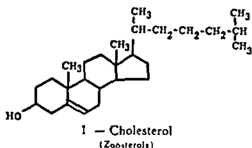
The "EVOCATOR" substances, emitted by certain "organizer" tissues for structural organization in early embryonic life are also claimed to behave like steroids

Numbering of carbon atoms and lettering of rings in parent hydrocarbon of the steroids

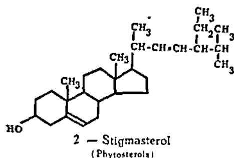


Cyclopentanoperhydrophenanthrene
(Norestrane)

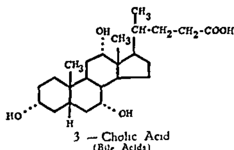
Representatives of the naturally occurring groups of steroids



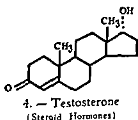
1 — Cholesterol
(Zoosterols)



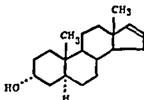
2 — Stigmasterol
(Phytosterols)



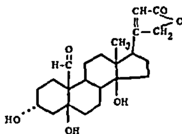
3 — Cholic Acid
(Bile Acids)



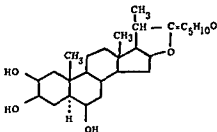
4. — Testosterone
(Steroid Hormones)



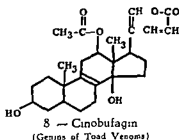
5. — Δ^{16}-Androstene-3 (α)-ol
(Odoriferous substances of testis)



6 — Strophanthidin
(Cardiac Aglucones)



7 — Digitogenin
(Digitalis Sapogenins)

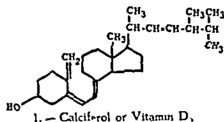


8 — Cinobufagin
(Genins of Toad Venoms)

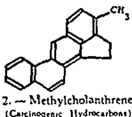
A number of other biologically important compounds are RELATED TO THE STEROIDS, although the original four ring system of norestrane is not maintained, for instance:

(1) The vitamin D group.
(2) Carcinogenic hydrocarbons.
(3) Morphine alkaloids (incl. codeine and its derivatives).
(4) Odoriferous substances of musk
(5) Artificial hormone-like substances (a. stilbene derivatives, b folliculoid carboxylic acids).

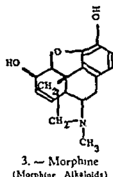
Representatives of biologically important groups of compounds related to the steroids



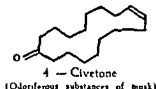
1. — Calciferol or Vitamin D_2
(Vitamin D group)



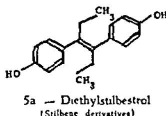
2. — Methylcholanthrene
(Carcinogenic Hydrocarbons)



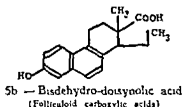
3. — Morphine
(Morphine Alkaloids)



4 — Civetone
(Odoriferous substances of musk)



5a — Diethylstilbestrol
(Stilbene derivatives)



5b — Bisdehydro-doisynolic acid
(Folliculoid carboxylic acids)

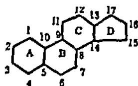
Representatives of the steroid hormones, themselves, occur in all the vertebrates and probably even in some invertebrates, plants and microbes. While zoosterols and phytosterols manifestly fulfil important functions in the lives of animals and plants, the biologic significance of steroid hormones has not been adequately studied, as yet, except in vertebrates.

Some steroids isolated from the testis proved to be odoriferous (musk-like odor) and there is a structural similarity between these and some of the constituents of musk which are responsible for its odor (Civetone).

The metabolism of the steroid hormones proceeds along somewhat different lines even in closely related vertebrates. Thus the metabolic endproducts of estradiol are different even in so closely related species as the rat and rabbit. Yet steroids show no definite species specificity as regards their pharmacologic actions For instance, estradiol stimulates the growth of the female accessory sex organs — while testosterone promotes the development of the male genitalia — in fish, amphibia, reptiles, birds, as well as in mammals.

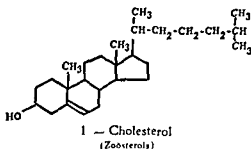
Even if we limit our considerations to the comparatively small group of the

Numbering of carbon atoms and lettering of rings in parent hydrocarbon of the steroids

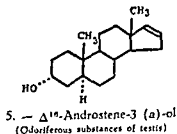


Cyclopentanoperhydrophenanthrene
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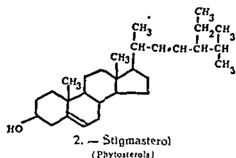
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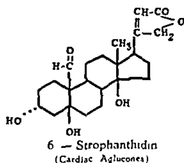
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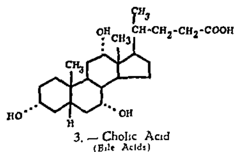
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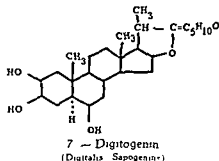
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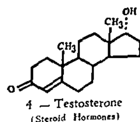
6 — Strophanthidin
(Cardiac Aglucones)



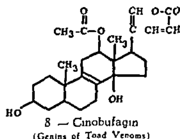
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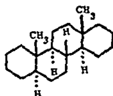


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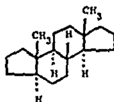
rings. If this is assumed to be behind the plane of the paper it is called "α" and is shown attached to the nucleus by a dotted line; in the reverse case it is designated by the letter "β"-and shown attached to the nucleus by a solid line. The other hydrogens on the nucleus — which do not deserve special attention — are customarily omitted from the formula.

It will be kept in mind that in the molecule of norestrane all 17 carbon atoms are saturated with hydrogen This means that 2 hydrogen atoms are attached to each carbon, except those (5, 10, 8, 9, 13, 14) which are common to adjacent rings. These carry only a single hydrogen whose spatial position is dependent upon that of the two rings (See: Nuclear isomerism, below.)

It is evident that in addition to the five nuclear parent hydrocarbons mentioned above, several other steric variations are possible; these are not mentioned here since they are of no obvious biologic significance It will also be kept in mind that if an additional carbon is introduced into the five membered ring D (thus transforming it into a six membered ring) or if one carbon is removed from the six membered ring A, thus transforming it into a five membered (pentane) ring, additional parent nuclear hydrocarbons can be prepared by partial synthesis but these will likewise not be discussed in this book since they are not proven to be *naturally occurring*. Suffice it merely to mention D-homoandrostane and pyroandrostane, the parent compounds of the series with a six-membered ring D and a five-membered ring A, respectively.



D-homoandrostane



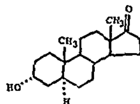
Pyroandrostane

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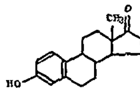
e.g., *androstane*-3(α)-ol-17-one·



Numeral indices, following the sign Δ, indicate the position of double bonds in the nucleus, where the linkage extends between carbon atoms not consecutively numbered, both numbers are recorded:

e.g. estrone =

$\Delta^{1,3,5,10}$-*estratriene*-3-ol-17-one



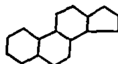
It will be noted that functional groups attached to a benzenoid ring are neces-

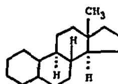
steroid hormones and their immediate derivatives, the variety of their functions in nature is truly astonishing. Such diverse phenomena are dependent upon the activities of steroid hormones as the pre- and postnatal growth and function of the accessory reproductive organs, the development of the ovaries and testes during the earliest stages of embryonic life, the striking nuptial coloring which certain fishes assume during the breeding season, the picturesque, sex-linked plumage pattern of many birds, the beard growth, baldness and muscular development of virile men, the crowing and the fighting instinct of the rooster, the woman's breast and the sexual drive. But as we shall see in the following sections, not only sex, but the development and metabolism of the entire body, as well as its resistance and adaptability to exposure and disease, are influenced by the steroid hormones of the gonads, the adrenal cortex and the placenta.

CHEMICAL TERMINOLOGY AND CLASSIFICATION OF THE STEROID HORMONES

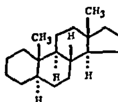
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The Parent Nuclear Hydrocarbons. — The parent compounds of all the steroids are saturated nuclear hydrocarbons, that is they consist exclusively of carbon and hydrogen and contain no double bonds. Depending upon the presence or absence of so-called angular methyl groups at C_{10} and C_{13}, and depending upon the relative steric (spatial) position of the four rings, a number of such nuclear hydrocarbons is possible. From the endocrinologist's point of view, the following are of the greatest importance:

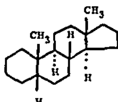

1. Norestrane



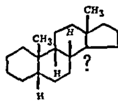
2. Estrane



3. Androstane



4. Etiocholane



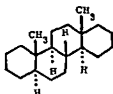
5. Urane
(9-epietiocholane)

The relative spatial position of two adjacent rings is difficult to show on a plain paper sheet, hence, it is customary to indicate it by the position of the hydrogen atom attached to the carbon atom which is common to two adjacent

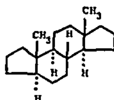
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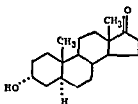
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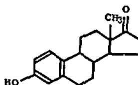
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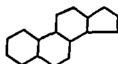
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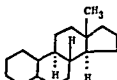
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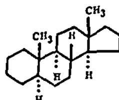
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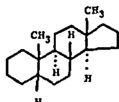

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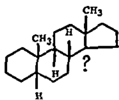
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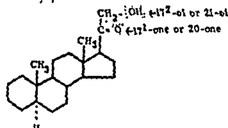
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applicable to all types of organic compounds, while the other is simpler and generally preferred in clinical literature.



17(β)-[1-keto-2-hydroxyethyl]-*androstane* or
Allo-pregnane-20-one-21-ol

Isomerism. — 1. NUCLEAR ISOMERISM. Consistent with the burden of evidence, it is assumed that in the androstane series, the substituents of each pair of adjacent asymmetric carbon atoms (i.e., 5.10, 9:10, 8:9, 8·14, 13·14) bear in space the opposite or "trans" relation to each other. Accordingly the two angular methyl groups fixed at C_{10} and C_{13} lie on the same side of the flat plane of the molecule (arbitrarily the near side) and serve as points of reference. As stated above, dotted lines are used to denote valence bonds which project behind the plane of the paper (the "trans" configuration with respect to the angular methyl groups), and solid lines to indicate those which stand forward (the "cis" configuration)

ETIOCHOLANE differs from ANDROSTANE only in the orientation about C_5. Accordingly it is formulated with a solid line issuing therefrom In androstane (as in allo-pregnane or 17(β)-ethyl-*androstane*) the relative positions of ring A B, B C and C D, is 'trans' throughout Such compounds are customarily designated as trans-trans-trans'.

In all naturally occurring *estranes* ring A is unsaturated, hence there is no hydrogen at C_5 Here the relative orientation of rings A and B cannot vary as ring A is flat and attached in the plane of the molecule The relative positions of rings B C and C D is again trans'

2 ISOMERISM OF THE SUBSTITUENTS AND OF THE SIDE-CHAIN For the designation of the steric arrangement of substituents at all centers of asymmetry, brackets follow the number of the substituted carbon atom. Contained therein is the index α or β: to denote the stereo-chemical relation to the rest of the molecule of a functional group (usually -OH) or a side-chain. β designates substituents which lie on the same side of the flat plane of the molecule as the angular methyl groups; α denotes the opposite direction. As regards such substituents, the terms β or "cis", on the one hand and α or "trans", on the other, are now used synonymously. All of the chemically stable, naturally occurring and biologically highly active derivatives of allo-pregnane are 17(β)-ethyl-*androstane* derivatives, while the 17(α)-ethyl-*androstane* compounds include the chemically labile, biologically less active, artificially prepared steroids

Common Names. — The correct chemical designation of steroids has the great advantage of giving complete details concerning their structure. However, as we saw above, these chemical terms are rather clumsy; hence, abbreviated common names are generally in use for the steroid compounds to which frequent reference is made. We have already encountered examples of these for instance, desoxycorticosterone and testosterone. Minor chemical changes in the molecular structure of such common compounds lead to derivatives which can still rather conveniently be referred to by modifications of the common name of the parent compound Thus methylation of testosterone yields "methyl-testosterone"; introduction of an ethynyl group into estradiol gives us "ethynyl-estradiol"; a compound which is isomeric with testosterone differing from the latter merely in the steric position of the hydroxyl, is called "iso-testosterone." etc

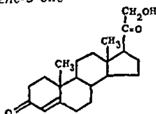
For the convenience of the reader, the structure formulæ, systematic chemical names and common names of the most frequently mentioned steroid compounds are listed (in alphabetic order) in the following table.

sarily in the same plane as the latter, hence in the above example for instance the — OH group is neither α, nor β.

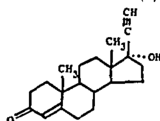
Saturated, nuclear hydrocarbons and their derivatives are designated by terms ending in "-ane", while unsaturated derivatives are designated with terms ending in "-ene" (compounds possessing two double bonds are "-dienes", those with three double bonds, "-trienes", etc.). The name of the parent hydrocarbon is printed in bold or italic letters to render it more conspicuous.

Etiocholane derivatives with a double bond at C_4 or C_5 are classified as androstenes. They could be designated as etiocholenes with equal justification since the relative position of rings A and B is equalized by such a double bond and the characteristic C_5 hydrogen eliminated.

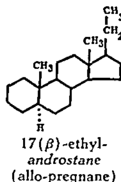
2. The Side-Chain. Aliphatic side-chains, both saturated and unsaturated, are designated by the name of the appropriate alkyl radical, the carbon atoms of which are numbered in sequence from the point of attachment. Functions substituted in the side-chain are named in accordance with the International Union Rules for the Naming of Organic Compounds. The prefixes hydroxy-, keto-, aldo- and carboxy- (respectively for alcohols, ketones, aldehydes and acids) are placed in square brackets with the name of the alkyl radical which precedes that of the nuclear hydrocarbons; in the absence of functions in the side-chain, the brackets are omitted, e.g., desoxycorticosterone = 17 (β) - [1-keto-2-hydroxyethyl] -Δ^4-*androstene*-3-one :



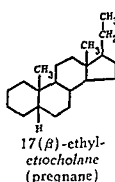
Ethynyl-testosterone = 17(β)-ethynyl-Δ^4-*androstene*-3-one-17(α)-ol :



Among the naturally occurring steroid hormones and their derivatives, alkyl radicals (other than the angular methyl groups) — if present — are attached only on carbon atom 17. The most important, naturally occurring alkyl substituted nuclear hydrocarbon derivatives are those of 17(β)-ethyl-*androstane* and 17(β)-ethyl-*etiocholane*, compounds also known under the shorter common names of allo-pregnane and pregnane, respectively :



17(β)-ethyl-
androstane
(allo-pregnane)



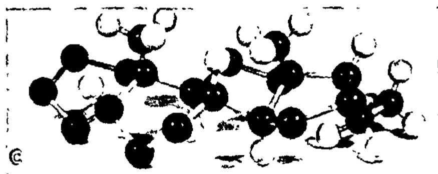
17(β)-ethyl-
etiocholane
(pregnane)

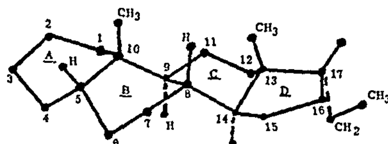
Derivatives of functions in the side chain are indicated by numerals with indices, the number gives the position of the alkyl radical, and the index that of the individual carbon atom in the side-chain to which the function is attached. In the pregnane, allo-pregnane nomenclature, the numeration of the carbon atoms of the nuclear parent hydrocarbon (which, with its two angular methyl groups goes up to 19) is merely continued so that carbon atom 17^1 becomes carbon atom 20 and 17^2, carbon atom 21. The following formula illustrates the two methods of numeration. That with indices for side-chain carbon atoms is more convenient, since it is generally

Structure	*Common Name*	*Systematic Chemical Designation*	*Natural occurrence*	*Predominant activity*
	iso-ANDROSTERONE	*androstane*-3(β)-ol-17-one	urine	testoid
	KENDALL'S CPD "E" 17-HYDROXY-11 DEHYDRO CORTICOSTERONE	17(β?)-[1-keto-2-hydroxyethyl]-Δ^4-*androstene*-3,11-dione-17(α?)-ol	adrenal	glucocorticoid
	METHYL-TESTOSTERONE	17(β)-methyl-Δ^4-*androstene*-3-one-17(α)-ol	not found in tissues	testoid
	PREGNANEDIOL	17(β)-[1(α)-hydroxyethyl]-*etiocholane*-3(α)-ol	urine	anesthetic (hormonally inactive)
	PREGNANEDIONE	17(β)-[1-ketoethyl]-*etiocholane*-3-one	urine	anesthetic (hormonally inactive)
	PREGNANOLONE	17(β)-[1-ketoethyl]-*etiocholane*-3(α)-ol	urine	anesthetic (hormonally inactive)
	PREGNENINOLONE or ETHYNYL-TESTOSTERONE or ANHYDRO HYDROXY-PROGESTERONE	17(β)-ethynyl-Δ^4-*androstene*-3-one-17(α)-ol	not found in tissues	luteoid
	PREGNENOLONE	17(β)-[1-ketoethyl]-Δ^5-*androstene*-3(β)-ol	testis	spermatogenic
	PROGESTERONE	17(β)-[1-ketoethyl]-Δ^4-*androstene*-3 one	ovary	luteoid
	TESTOSTERONE	Δ^4-*androstene*-3-one-17(α)-ol	testis	testoid

LIST OF MOST COMMONLY MENTIONED STEROID HORMONES

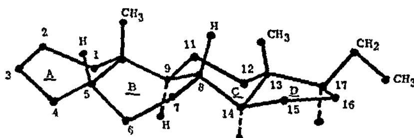
Structure	*Common Name*	*Systematic Chemical Designation*	*Natural occurrence*	*Predominant activity*
	ADRENOSTERONE	Δ^{4}-*androstene*-3,11,17-trione	adrenal	testoid
	ANDROSTERONE	*androstane*-3(α)-ol-17-one	urine	testoid
	CORTICOSTERONE	17(β)-[1-keto-2-hydroxy-ethyl]-Δ^{4}-*androstene*-3-one-11(β)-ol	adrenal	gluco-corticoid
	DEHYDROCORTICOSTERONE	17(β)-[1-keto-2-hydroxy-ethyl]-Δ^{4}-*androstene*-3,11-dione	adrenal	gluco-corticoid
	DEHYDRO-*iso*-ANDROSTERONE	Δ^{5}-*androstene*-3(β)-ol-17-one	urine	testoid
	DESOXYCORTICOSTERONE or 11-DESOXYCORTICOSTERONE	17(β)-[1-keto-2-hydroxy-ethyl]-Δ^{4}-*androstene*-3-one	adrenal	mineralo-corticoid
	ESTRADIOL	$\Delta^{1,3,5,10}$-*estratriene*-3,17(α)-diol	ovary placenta testis urine	folliculoid
	ESTRIOL	$\Delta^{1,3,5,10}$-*estratriene*-3,16(β), 17(α)-triol	placenta urine pussy-willows	folliculoid
	ESTRONE	$\Delta^{1,3,5,10}$-*estratriene*-3-ol-17-one	urine testis placenta palm kernels	folliculoid
	ETIOCHOLANOLONE	*etiocholane*-3(α)-ol-17-one	urine	anesthetic (hormonally inactive)
	HYDROXY-PREGNENOLONE	17(β)-[1-keto-2-hydroxy-ethyl]-Δ^{5}-*androstene*-3(β)-ol	not found in tissues	mineralo-corticoid





C-17(α)-ethyl-ETIOCHOLANE. Note that steric arrangement of the 4 rings is the same as in previous compounds, except for the relative position of ring A to ring B. Correspondingly, the hydrogen at C_5 is in beta position. ('Coprostane type'.) The ethyl side-chain is attached in alpha position

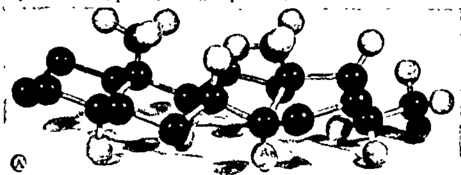


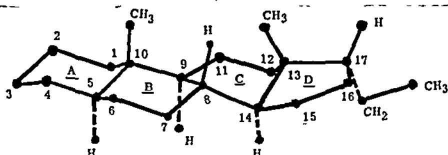


D-17(β)-ethyl ETIOCHOLANE. Steric arrangement of the steroid ring system is the same as in previous compound, but the side-chain is attached in beta position.

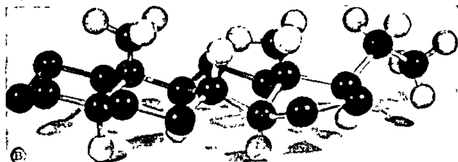
SPACE MODELS OF THE PRINCIPAL STEROID TYPES

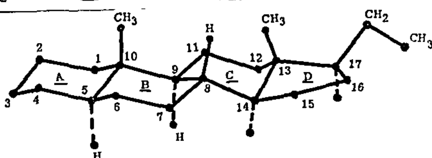
The following are actual photographs of space-model reconstructions of the 4 principal hydrocarbons from which the steroid hormones are derived. Under each photograph is a schematic drawing, showing the connections (valence bonds) between the various atoms, viewed precisely from the same angle as the corresponding photographs. In order to avoid too much overlap between individual atoms, all four molecule reproductions have been photographed and drawn from a *position almost parallel with the "plane" of the molecule.*





A -17(α)-ethyl-ANDROSTANE Note alpha position of the hydrogens at C_5, C_9 and C_{14} This is the so-called "trans-trans-trans" arrangement ('cholestane type') The ethyl side-chain is also attached in the alpha position





B -17(β)-ethyl-ANDROSTANE. The steroid skeleton is the same as in the previous compound, but the ethyl side-chain is attached in the beta position.

from that particular gland. It merely *suggests that the compound simulates* the gland's activity, and this is true by definition. It would be misleading, for instance, to designate hormones of the testoid type as "testicular hormones" since such compounds are also elaborated by the adrenal cortex and probably even by ovarian and placental tissues. It would be equally misleading to term them "androgenic" since the most potent natural "androgen" testosterone, causes testis atrophy in experimental animals. Thus, far from being masculinizing it is actually "demasculinizing." Similarly, in many animal species, the so-called "estrogens" do not in themselves cause *estrus or heat without simultaneous* progesterone treatment, hence the latter hormone could be called "estrogenic" with almost equal justification. Furthermore, folliculoids interrupt the estrous cycle in the intact rodent so that they are actually "anti-estrogenic" under ordinary circumstances of bioassay. The term "gynaecogenic" is no more *adequate for them since they cause* ovarian atrophy.

In the light of the above considerations, it appears unsatisfactory to designate these hormones either according to their source of origin or on the basis of one particular action on a certain target organ. Hence, we give preference to the terminology which is based *upon the natural classification* of the independent steroid hormone actions according to the gland whose function they simulate.



Steroid hormone anesthesia. Photograph of a female rat (body weight 70 gm) under profound anesthesia after intraperitoneal administration of 10 mg of progesterone in 0.5 cc of oil. Note marked muscular relaxation.

Subordinate Actions. — As indicated above, each independent action has numerous distinct subordinate manifestations inasmuch as it affects a variety of target organs. Thus a folliculoid hormone (e.g., estradiol) which produces vaginal cornification in the rodent, invariably — and to a degree which runs parallel with the intensity of its effect on the vagina — causes enlargement of the uterus, the oviducts, the adrenals, the nipples, hyperemia of the monkey's sex skin, atrophy of the testes, etc. All these manifestations are termed subordinate actions in order to emphasize that they are dependent *upon, and the direct consequence of,* a single independent action (in this case, the folliculoid action). In the same sense, the ability to stimulate the seminal vesicles, the prostate, the capon's comb, etc., are subordinate to the testoid action. For the sake of simplicity, organ growth stimulating and inhibiting subordinate actions are designated by the

PHARMACOLOGIC TERMINOLOGY AND CLASSIFICATION OF THE STEROIDS

Definition and Outline. — We have seen that the complicated chemical structure of the steroid molecule made it necessary to devise a rather intricate system of terminology and classification. When we come to consider its complex pharmacologic characteristics we shall find that these also require careful systematization before they can be clearly understood or even rationally enumerated.

The manifold pharmacologic activities of the steroids and the fact that almost any of them possess an apparently unpredictable combination of such activities, tend to give the impression of a complete lack of orderliness. In other words, it appears as though there were no correlation between the chemical structure of a compound and its pharmacologic activities (pharmaco-chemical correlations), nor between the several pharmacologic effects themselves (pharmaco-pharmacologic correlations) which a single compound may exhibit. Yet, certain general lawful correlations of this kind have already been elucidated and found to hold true for all hormone-like steroids examined up to the present time. This type of study is perhaps the most fascinating and, from a practical point of view, the most important aspect of contemporary steroid hormone research An almost unlimited number of steroids could be made available by partial synthesis from the known compounds, but since the only value of these compounds is their therapeutic efficacy we must learn more about the structural prerequisites of their pharmacologic activities in order to direct the work of the synthetic chemists into profitable channels.

The following paragraphs are merely a sketch of the fundamental prerequisites for the study of this important field. They attempt to outline the main principles according to which the actions of steroid hormones are named and classified.

Independent Actions. — The basic principle according to which the pharmacologic activities of steroids are classified is that certain actions are independent of each other while others are merely the subordinate manifestations of such independent actions and hence dependent upon them. It must be clearly understood that independent actions are characterized by the fact that every one of them can be exhibited independently of any of the others; that is to say, there is no direct parallelism between the degree to which a compound exhibits the various independent actions. In this sense we recognize the independent nature of the following actions :

(1) Folliculoid (estrogenic, gynæcogenic, estromimetic or follicular-hormone-like).
(2) Testoid (androgenic, andromimetic or male hormone-like).
(3) Luteoid (progestational, corpus luteum-hormone-like)
(4) Corticoid (adrenal-cortical hormone-like)
(5) Spermatogenic (having the ability to stimulate the spermatogenic epithelium and mainly to protect it against atrophy caused by deficiency in gonadotrophic hypophysoid hormones)
(6) Renotrophic (nephrotrophic, having the ability to increase kidney size due mainly to hypertrophy of the convoluted tubules)
(7) Anesthetic
(8) Anti-fibromatogenic (Inhibiting fibroma formation by folliculoids — see p 370)

It will be noted that for those independent actions which imitate the function of an organ of internal secretion, terms are used which suggest a specific connection with that particular endocrine gland The Greek ending "-oid", which is added to the name of a gland, means "similar to" without implying that the hormone is necessarily derived

which they are placed on top as the most active folliculoid and anesthetic compound respectively. The three remaining compounds slowly lose height in both directions with approximately the same slope. Thus the curve described by the position of any steroid in the table exhibits a single maximum.

The table expresses the empirical fact that only folliculoid or anesthetic potencies may be exhibited to the exclusion of all other independent actions, since these two are on the outer limits of the system and hence do not have to overlap with other effects. Compounds not included in this table also obey the same rules although, of course, depending upon the degree of their potency, they range above or below the curves given here. Thus ethynyl-estradiol, which is somewhat more folliculoid than estradiol, describes a line parallel with that of estradiol although somewhat higher than the latter, while pregnenolone, a compound having an activity which is qualitatively similar but quantitatively inferior to that of progesterone, parallels the curve of the latter at a somewhat lower level. Acetoxypregnenolone, a comparatively inactive corticoid, parallels the desoxycorticosterone acetate curve in a similar manner, and so forth. Among all steroids studied no exception could be found to the rule that all compounds describe curves with a single maximum when inserted in this system.

Disregarding all possible a priori arguments from chemical relationships, statistical analysis showed that the regularities in the whole scheme would occur by chance only in 1 out of 2,304 trials, allowing for the selection of the top entry in each column and giving no "credit" for possible orderliness in the compounds found inactive in each type of test. Hence, it may be said that this particular arrangement is not due to chance but is apparently dependent upon certain inherent natural relationships between the steroids. The main weakness of the classification so far detected is that the activity curve of a certain compound may skip one or more points on the curve, perhaps because this particular action is so "masked" that it is not detectable with our bioassay methods.

The biologic significance of these correlations among the steroids is not easy to interpret. It may be that the molecular structure necessary for any one activity necessarily carries within itself other pharmacologic properties and that the intensity of these decreases in direct proportion to their distance from the primary activity in the table. It is also possible that the compound placed at the peak of any one curve is partly transformed in the body into compounds with neighbouring actions which in turn yield smaller amounts of steroids in the columns next to them. Thus the degree of activity would gradually diminish in proportion to the distance in the tablefrom the position of the original compound injected In this sense the pure folliculoids and anesthetics might be considered as metabolic end-products incapable of re-transformation into compounds occupying more central positions in the table. This is graphically expressed by their marginal position and the fact that the most active folliculoids and anesthetics exhibit no other activities. That a compound may skip a point on the curve could be explained by assuming that certain steroids may go through a pharmacologically inactive stage during their metabolism.

Considering the limited data available at this time, it would scarcely be justified to base any far-reaching speculations on the regularities observed. The only purpose of the table is to direct attention to the fact that if the steroids are arranged according to the degree of their folliculoid activity, they fall into a natural system which permits — within limits — a prediction of their other activities.

Systematic table of the steroids

FOLLICULOID	TESTOID	LUTEOID	CORTICOID	ANAESTHETIC
ESTRADIOL	TESTOSTERONE	PROGESTERONE	DESOXYCORTICOSTERONE ACETATE	PREGNANEDIONE
TESTOSTERONE	PROGESTERONE	DESOXYCORTICOSTERONE ACETATE	PROGESTERONE	DESOXYCORTICOSTERONE ACETATE
PROGESTERONE	(desoxycorticosterone acetate)	TESTOSTERONE	(testosterone)	PROGESTERONE
DESOXYCORTICOSTERONE ACETATE	(estradiol)	(estradiol)	(estradiol)	TESTOSTERONE
(pregnanedione)	(pregnanedione)	(pregnanedione)	(pregnanedione)	ESTRADIOL

In constructing this table, the most active representatives of five independent actions have been selected and arranged from left to right according to decreasing order of folliculoid potency (Since the most potent representatives of the renotrophic and spermatogenic series have not been definitely identified as yet, these actions are not considered here. However, according to the folliculoid effect of the known prominent representatives of these groups, they should both be inserted next to testosterone.) It will be noted that the folliculoid activity of all these compounds, except estradiol, is "masked" and detectable only under certain experimental conditions. Furthermore, for the purpose of this discussion prostatic enlargement is considered sufficient for the demonstration of testoid activity. Desoxycorticosterone acetate has been chosen as the most active representative of the corticoid series as it is the only highly active member of this group which has been adequately studied for all five independent actions. In each column representing a certain type of activity the inert compounds are inserted in brackets below the active compounds of the group.

When the steroids are so arranged according to decreasing folliculoid activity in the first line of the table, the most active representatives of the folliculoid, testoid, luteoid, corticoid and anesthetic compounds appear in the order stated. The second most active representatives of each of these five activities were placed in the second line, third place being given to the next most active compounds, and so forth.

Perusal of the table indicates that, if the steroids are arranged in the first column according to decreasing order of folliculoid activity, they are automatically in increasing order of anesthetic potency. The position of each steroid was traced by a line through the five columns. This revealed that estradiol and pregnanedione are at the bottom of the graph, except in the column in

(2) The dose level at which the mixture is administered.

(3) The target organ whose response to the mixture is studied.

To illustrate the importance of the RATIO of two interacting steroids in a mixture, suffice it to mention that small doses of estradiol enhance certain actions of progesterone (e.g., progestational proliferation of the endometrium, vaginal mucification, deciduoma formation, maintenance of pregnancy in ovariectomized females) while large doses of the same folliculoid completely prevent these luteoid effects.

The DOSAGE, in which a given mixture is administered, is likewise important. Thus, in spayed rats, a solution containing small amounts of estradiol and large quantities of progesterone causes continuous vaginal cornification at low, but mucification at high dose levels. In other words, at the low daily dose level the folliculoid, while at the high dose level the luteoid effect of the mixture predominates.

Similarly, if a solution containing small doses of estradiol and large doses of testosterone is given to intact male rats, it causes especially pronounced atrophy of the seminiferous tubules at low daily dose levels, but results in no tubular damage at high dose levels Apparently, at the low dose level, the anti-spermatogenic action of estradiol and of testosterone is additive, while at high dose levels, the anti-spermatogenic effect of estradiol is counteracted by the spermatogenic property of testosterone In this antagonism the dose of estradiol is of no great importance This folliculoid appears to act upon the testis by inhibiting the gonadotrophin production of the hypophysis and even doses many times greater than the minimal amount required for this "functional hypophysectomy" cannot accomplish more than a surgical hypophysectomy can Since moderate doses of spermatogenic steroids (e g., testosterone) maintain the tubules even after complete ablation of the hypophysis it is understandable that they are equally effective in rats in which the testis atrophy is produced by any dose of estradiol.

Other things being equal, the effect of a steroid hormone mixture is largely dependent upon the TARGET ORGAN whose response we study Thus, desoxycorticosterone acetate or ethynyltestosterone, given in high doses, completely inhibit the vaginal cornification normally produced by estradiol. Hence, as regards this target organ, they are antagonists of folliculoids. On the other hand, these same compounds do not inhibit the anti-spermatogenic effect of estradiol

Such observations are of fundamental importance. They clearly demonstrate that steroids which antagonize folliculoid actions, do not completely annul them (as an acid would neutralize an alkali, or glucose would antagonize all the manifestations of insulin hypoglycemia); they merely interfere with certain effects upon specific target organs Indeed, we know of no instance in steroid pharmacology where all effects of a certain compound would be completely nullified by simultaneous treatment with another steroid

Manifest and Masked Actions. — We have seen that chemically pure steroid compounds may exhibit several independent pharmacologic actions. We also learned that in mixtures containing two steroids — each exhibiting a different independent action — the effects of the two components may be synergistic or antagonistic, depending upon the ratio, the dose and the target organ. In view of these facts, it is not surprising that two independent actions of a single chemical substance may likewise influence each other. Obviously, here, the ratio of the two activities is fixed since both actions are due to the same molec-

INTERRELATIONS BETWEEN THE VARIOUS PHARMACOLOGIC PROPERTIES OF THE STEROIDS (PHARMACO-PHARMACOLOGIC INTERRELATIONS)

Definition and Outline. — By pharmaco-pharmacologic interactions among the steroids we understand the property of two independent actions to influence each other. The subordinate effects of any one independent action cannot detectably influence each other since they are only different manifestations of the same pharmacologic property. On the other hand, if an animal is simultaneously treated with two steroid compounds, having different independent actions, one compound may inhibit or augment the effects of the other. An inhibition may result from a simple diminution or abolition of the effect (quantitative inhibition), but it may also be due to a modification of the action (qualitative alteration). In the *case of an augmentation or synergism,* there may be pure summation (mere addition of two similar actions) or true potentiation (synergism greater than could be expected by merely adding the two effects).

Even two independent actions exerted by a single chemical compound may mutually influence each other. In this event, treatment with one compound will cause a complex response, namely the resultant of this interaction.

Knowledge of the pharmaco-pharmacologic interrelations is of great practical value, since it is often possible to increase the selectivity of hormone actions by using drug combinations which accentuate the desired property but minimize undesirable side effects.

Synergisms and Antagonisms. — Synergisms, in the sense of mere SUMMATION of effects, are comparatively common among the steroid compounds In fact most steroids which have certain actions in common, are additive as regards these pharmacologic properties Thus, the effect of *estradiol and estrone* upon the vagina, or that of testosterone and androsterone upon the seminal vesicles, is additive if the compounds are given simultaneously in submaximal doses.

On the other hand, there are only few instances of clear-cut POTENTIATION of steroid hormone actions. As a pertinent instance, we may mention the potentiation of the luteoid effect of progesterone by folliculoids. The progestational transformation of the endometrium, the mucification of the vaginal epithelium, the proliferation of the mammary glands, the relaxation of the symphysis pubis and the production of deciduomas, following endometrial trauma, are all characteristic effects of luteoid compounds However, enormous doses of progesterone are required in order to elicit these changes unless the test animals are pretreated, or simultaneously treated with minute doses of *folliculoids. Therefore, in all these in*stances, we may well speak of a true potentiation of the luteoid compounds by the folliculoids.

There are many more instances of ANTAGONISMS between steroid hormones. Thus, the ability of corticoids to maintain adrenalectomized animals, is counteracted by simultaneous treatment with folliculoids. This is merely due to the fact that the latter are very toxic for the adrenal-deficient animal and raise its corticoid hormone requirement *The adrenal-cortical enlargement eli*cited by folliculoids is also inhibited by corticoids. Similarly, the testis atrophy produced by folliculoids in normal males is diminished, or even completely prevented, by concurrent treatment with spermatogenic steroids, such as pregnenolone

It is important to realize that the manner in which two steroid hormones *influence each other's actions depends* upon three factors ·

(1) The ratio of the two compounds in a mixture.

fundamental consideration, namely the distinction between simple and complex activities. Certain steroids appear to possess only their manifest actions which are detectable under all circumstances. Others are endowed with a multiplicity of pharmacologic properties, some of which are manifest while the rest are masked or modified. The compounds belonging to the former category are pharmacologically "SIMPLE" since they possess only overt properties. The compounds of the second category are pharmacologically "COMPLEX" because, in addition to their overt manifestations, they possess masked properties which may modify the others. As previously mentioned, the best representatives of "simple" actions are found among the predominantly folliculoid and anesthetic compounds; hence, the problem can best be clarified by making a pharmacologic comparison between these and the main representatives of all other independent groups of our classification

It appears that the predominantly folliculoid compounds differ from the principal representatives of all other independent groups in that there are no qualitative differences in the pharmacologic properties of hormonally active estrane compounds of high folliculoid potency or their synthetic derivatives. Indeed even non-steroid compounds (e g , the stilbene derivatives) are qualitatively equal, although quantitatively the degree of their activity varies. In sharp contrast with this uniformity the principal representatives of all other independent groups possess highly variable properties. Thus the two most active natural testoids, testosterone and androsterone, differ markedly in that the former is comparatively more active in stimulating the capon's comb and the rat's seminal vesicles, while the latter possesses a relatively greater pro-prostatic effect Similarly, among the corticoids, corticosterone has a greater gluco-corticoid and desoxycorticosterone a greater mineralo-corticoid activity.

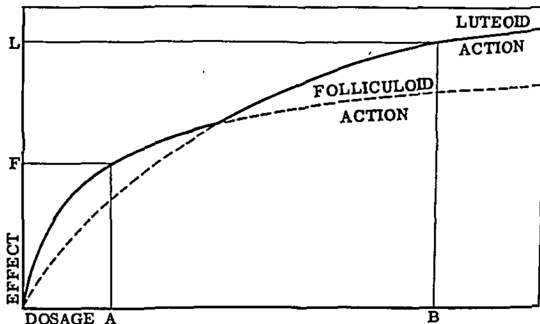
The comparative pharmacologic simplicity of the primarily folliculoid compounds is especially striking if we consider that none of the active estranes show any pharmacologic overlap with the hormonal properties characteristic of other independent groups. Neither estradiol nor estrone, estriol or even the stilbenes possess the slightest luteoid, corticoid, testoid, spermatogenic or renotrophic activity. This is very remarkable if we remember that not a single compound is known which would selectively exhibit any one of these latter five activities. It should be remarked parenthetically that the seminal-vesicle-increasing effect of hormonally active estranes is by no means a "testoid" action, as it is merely due to disproportionate fibro-muscular growth.

There is only one other independent action which may be considered to be "simple" in the sense in which the word is used here This is the anesthetic effect which is selectively exhibited by some steroids (e.g., pregnanedione) to the exclusion of all known hormonal properties.

All the steroids with other independent actions [corticoid, luteoid, testoid, spermatogenic or renotrophic] are pharmacologically complex. No compound is known which would exhibit any one of these latter activities in a pure form, without possessing some other action as well. It is impossible therefore to decide whether it is merely coincidental that all known steroids with predominantly corticoid, luteoid, testoid, spermatogenic or renotrophic activity, exhibit some subsidiary actions or whether these pharmacologic effects themselves are inherently dependent upon the simultaneous manifestation of several activities In other words, the problem is, are these actions single tones or chords? Should compounds become known which possess only one of these independent activities, then this action will

Graph illustrating interrelations between manifest and masked activities of steroids.

If a mixture containing certain proportions of a folliculoid compound (e g , estradiol) and a luteoid substance (e.g , progesterone), or a single compound possessing both these activities (e.g , testosterone), is administered at various dose levels, the folliculoid actions (F) will predominate at low doses (A), while at high dose levels (B), the luteoid (L) actions become manifest As the graph implies, this may be due to differences in the slope of the dose-effect relationship of luteoid and folliculoid activity respectively, so that at low dose levels, the former effect would be "masked' by the latter.



ular structure, only dose level and target organ are subject to variation.

For the analysis of such pharmacologic interactions between two independent properties — whether exhibited by a single steroid or a mixture — it is convenient to distinguish between manifest and masked activities. An activity is considered to be MANIFEST, or overt, under all experimental conditions in which it is detectable. Thus, for instance, the testoid activity of testosterone is manifest if the compound is administered to immature, or castrate rats

Certain steroid hormone actions are not demonstrable under ordinary circumstances, yet they are real since they become evident under special experimental conditions In such cases, we speak of MASKED activities and assume that the pharmacologic property is inherent in the compound though not in a manifest form. For instance, in testosterone, the vagina-cornifying effect is not detectable under ordinary conditions of bioassay because it is masked by the vagina-mucifying effect. During the first days of treatment, however, the compound causes a transitory vaginal cornification in the spayed or immature female rat, in hypophysectomized females, the cornification usually becomes permanent. In this manner, it is possible to "unmask" an otherwise hidden property. It was to be expected that any vagina-cornifying action of testosterone would be masked, under the standard experimental conditions prevailing in the spayed female, since even the most potent folliculoids (e g , estradiol or estrone) are inactivated in this respect by simultaneous administration of a vagina-mucifying compound such as testosterone (see above)

Simple and Complex Actions. — The differentiation of manifest and masked properties leads us to another

they are exhibited most readily (at the lowest dosage level) by compounds *which are predominantly folliculoid.*

Many of the inhibitable folliculoid actions are not manifest in compounds with other independent activities, since the latter can counteract or "mask" the former even when produced by pure folliculoid estrane derivatives. Thus testosterone shares with the folliculoids such non-inhibitable actions as the anti-thymus, anti-castration cell, pro-mammary gland and plumage-feminizing effects. These cannot be inhibited by testosterone even when they are elicited by estradiol itself. On the *other hand, testosterone elicits little* or no persistent vaginal cornification, pro-adrenal or anti-spermatogenic ef*fects and these are precisely the prop*erties of estradiol which are inhibited by simultaneous testosterone administration. *Hence, the evidence available* at this time, is in agreement with the assumption that all steroid hormones possess some folliculoid actions (see: Systematic Table of the Steroids) but that among these, only the non-inhibitable properties are always manifest, while the others are demonstrable only under certain circumstances.

Selective Inhibition. — The different *subordinate manifestations* of one independent action of a certain steroid are not always equally inhibited by another *independent action of* the same compound. Thus, for instance, ethynyl-testosterone can cause vaginal *mucification and progestational trans*formation of the endometrium, that is, changes dependent upon the predom*inance of its luteoid over its folliculoid* properties Unlike progesterone, ethynyl-testosterone is anti-spermatogenic *at all dose levels, that is, in this respect* its folliculoid properties predominate Other luteoids (e g , progesterone) *inhibit both their own folliculoid* actions and those of simultaneously given folliculoids, not only on the vagina (causing mucification rather than cornification) and uterus (progestational rather than estrus changes) but also on the testis (inhibition of antispermatogenic effect). Hence, we may *conclude that in the case of ethynyl*testosterone, which possesses both folliculoid and luteoid effects, the former *are selectively inhibited by the latter on* some target organs (e g , vagina, uterus) but not on others (e.g , testis).

INTERRELATIONS BETWEEN THE PHARMACOLOGIC PROPERTIES AND THE CHEMICAL STRUCTURE OF THE STEROIDS (PHARMACO-CHEMICAL INTERRELATIONS)

Definition and Outline. — The study of the correlations between the chemical structure and pharmocologic *activity of the steroids is also of great* practical importance. It is the only means by which the efforts of the chemists, *interested in the synthesis of bio*logically useful steroids, can receive a promising orientation. Very little has been done *along these lines as yet, apart* from a fairly systematic study concerning pharmaco-chemical correlations among the anesthetic steroids and among the testoid androstane derivatives

A possible explanation for the deplorable lack of interest displayed in this field is that when pharmacologists attempt to study correlations between chemical structure and *biologic action* in any series of related compounds, they are often discouraged by striking *instances* which *appear to contradict* all their conclusions An apparent instance of this type has already been *encountered in the steroid field, inas*much as certain stilbene derivatives share all the actions of the natural folliculoids (*claims for allegedly corticoid* and luteoid stilbene derivatives have been refuted) although they possess *an entirely different chemical struc*ture It must be kept in mind, however, that pharmaco-chemical correla-

be proven to be simple; until then, however, we must consider the possibility that the actions themselves are inherently complex.

Let us illustrate this point. As we have stated before, the main (luteoid) *activity of progesterone, the principle* representative of the luteoids, is greatly enhanced by minute quantities of folliculoids. It has also been demonstrated that progesterone itself possesses some folliculoid effect although it is masked under ordinary circumstances It is quite possible, therefore, that what we consider the "luteoid" or "progestational" *effect is inherently* the *sum* of a slight folliculoid and some other (yet unknown) pharmacologic potency. Until quite recently, when very large doses of progesterone were assayed, this compound was believed to be inert unless given in conjunction, or following pretreatment with folliculoids. It is conceivable that the manifestation of luteoid activity, in the case of treatment with progesterone alone, necessitates unduly large doses merely because great amounts have to be administered to supply the folliculoid potency required for the manifestation of the luteoid effect.

In the light of these considerations, it appears possible that important hormonal *activities may* be detected in *some apparently inert steroids* (e.g., pregnanedione) by combined administration with other substances which complement their effect. This type of activation is by no means without precedent in *endocrinology Thus, for instance*, the luteinizing hormone of pregnancy urine has no effect upon the granulosa cells in the ovary of the hypophysectomized rat unless some preliminary development is *first induced by treatment* with the follicle-stimulating hormone. At first sight it may appear that the so-called "x-substance" (which can be extracted from testis tissue and is probably identical with some *of the* highly unsaturated fatty acids) belongs to this group, inasmuch as it is inactive in itself but increases the effect of testoids. Yet this type of activation is somewhat different; it manifests itself only if the two compounds are *injected* at the same *site* and *hence* it is probably due merely to the resultant delay in hormone absorption.

Inhibitable and Non-Inhibitable Actions. — We have already had occasion to mention the existence of antagonisms between different steroid hormones and the fact that even the diverse actions of a single chemical compound *may likewise antagonize each other in* such a manner as to produce "masked" or modified actions. Indeed, in certain instances, such a mutual antagonism between two properties of the same molecule may be regarded as almost definitely proven. For instance in the case of desoxycorticosterone, which possesses both corticoid and folliculoid actions, it may be taken for granted that the anti-adrenal effect, which is subordinate to the former, and the proadrenal effect, characteristic of the latter property, partly antagonize each other. Similarly the vagina-cornifying property of progesterone is usually inhibited by its own mucifying effect, which — as was previously mentioned — is so strong that it even inhibits the *cornification* otherwise caused by estradiol However, some actions of estradiol (e g., the anti-thymus, anti-Leydig-cell and anti-castration-cell effects) are not inhibitable by simulta*neous treatment with other steroids*

In view of these considerations it is interesting to note that all the noninhibitable folliculoid actions are common to all steroid hormones Con*versely (with the exception of the* anesthetic effect which is not strictly speaking a hormone-like property), all the adequately studied actions common to all steroid hormones are primarily *folliculoid properties, inasmuch as*

QUALITATIVE CHANGES IN PHARMACOLOGIC ACTIVITY MAY ONLY BE EFFECTED BY ALTERING CARBON TO CARBON LINKAGES OR THE STATE OF OXIDATION of a steroid.

Pharmaco-Chemical Rules Within Each Category of Independent Actions. — *In this section we wish to* review only the most important pharmaco-chemical correlations which appear to be responsible for each of the independent pharmacologic actions. We shall not repeat the general rules mentioned in the previous chapter, but it must be remembered that they also apply to all the independent actions.

Since only very little work has been done under strictly comparable bioassay conditions, most of the available data of the literature are unsuitable for this type of analysis. We summarize a few of the main facts, merely as examples of how such pharmaco-chemical correlations can be worked out.

The most convincing type of evidence is derived from the comparative bioassay of two compounds differing from each other only with respect to one detail in chemical structure. For instance, the comparison of two isomeric alcohols can show us the importance of the steric position of the hydroxyl in question. Comparison between a hydroxyl and the corresponding ketone tells us which of these two groups are more likely to increase potency. It must be realized, however, that these correlations are necessarily valid only if the rest of the molecule is identical. For instance, a 3-hydroxyl may be more advantageous for the production of a certain effect than the corresponding 3-ketone if the rest of the molecule has a certain structure, while the reverse relationship may obtain after introduction of another group at a different part of the molecule. Extrapolations to other steroids are permissible only if a certain pharmaco-chemical relationship has been noted in a large number of compounds.

The folliculoids. — All naturally occurring pharmacologically pure (simple) folliculoids are ESTRANE derivatives and conversely, all biologically active estrane derivatives are *pure* folliculoids devoid of any other activity.

A SIDE-CHAIN AT C_{17} does not necessarily decrease folliculoid activity in the estrane series and under certain circumstances, it may even increase it as in ethenyl-estradiol or ethynyl-estradiol.

All naturally occurring pure folliculoids are comparatively highly UNSATURATED, having three or more double bonds and a PHENOLIC HYDROXYL group But neither the high degree of unsaturation, nor the phenolic hydroxyl, are essential for some degree of folliculoid activity in a compound having other independent actions as well. This is shown, for instance, by androsterone which is completely saturated, and devoid of a phenolic hydroxyl, yet possesses (usually masked) folliculoid activity. The unimportance of the phenolic hydroxyl has also been proven within the estrane group since $\Delta^{5,7,9:10}$-*estratriene-3(a), 17*-diol *is strongly folliculoid* though less so than estradiol

It has been claimed that the DISTANCE BETWEEN THE TWO POLAR OXYGENS (e.g., 3 and 17 in estrone and estradiol) is the chief prerequisite of folliculoid activity; however, some of the carcinogenic hydrocarbons, triphenylchlorethylene etc., are folliculoid although they possess no oxygen.

Attachment of a METHYL group at C_{10} is compatible with folliculoid potency as shown by the androstane and allopregnane derivatives which possess this activity.

OPENING OF RING D is compatible with the highest degree of folliculoid activity as shown by the doisynolic acid derivatives.

The corticoids.— A 2-CARBON ATOM SIDE-CHAIN AT C_{17} proved essential for corticoid activity in all compounds tested.

tions established for a certain chemical group do not necessarily hold for another series. Let us not forget that in many other fields of pharmacology (morphine derivatives, adrenaline derivatives, etc) important new drugs became available to the medical profession only as a result of painstaking pharmaco-chemical studies, which gave a lead to the synthetic chemist concerning the type of compound which is likely to possess the desired pharmacologic property. We hope to show that even in the complex steroid molecule certain definite pharmaco-chemical correlations are already clearly demonstrable.

Pharmaco-Chemical Rules Applicable to All or Several Independent Actions. — ALL ETIOCHOLANES ARE DEVOID OF HORMONAL ACTIONS. This *is also true of all* C_{17} *substituted* etiocholanes such as the pregnanes. Etiocholanes may however, exhibit a pronounced anesthetic effect. Androstane configuration at C_5 or unsaturation at Δ^4 or Δ^5, which removes the C_5 hydrogen characteristic of the etiocholanes, renders the steroid potentially capable of hormonal actions.

A 6 MEMBERED RING D IS COMPATIBLE BOTH WITH ANESTHETIC AND HORMONAL ACTIVITY as shown by the example of the D-homoandrostanes.

NO STEROID POSSESSING A LONG C_{17} SIDE-CHAIN HAS ANY HORMONAL OR ANESTHETIC ACTIVITY. 5 and 6 carbon-side-chain compounds have not been adequately studied as yet, but "21-ethyl-progesterone", that is, 17(β)-[1-ketobutyl]-Δ^4-*androstene-3*-one with a 4 carbon atom side-chain, proved highly active as an anesthetic and also exhibited some folliculoid activity, while Δ^4-nor-cholestene-3,25-dione, with a 7 carbon atom side-chain, proved entirely inert.

The STERIC POSITION OF THE SIDE-CHAIN IS VERY IMPORTANT, the natural 17(β) position being usually preferable. Thus natural, that is 17(β)-progesterone and 17(β)-desoxycorticosterone are highly active as luteoids and corticoids respectively, while the corresponding isomeric 17(α)-alkyl compounds are practically inert. The synthetic 17(β)-alkyl derivatives are also very potent as shown by 17(β)-ethynyl-testosterone, 17(β)-ethynyl-estradiol, 17(β)-methyl-testostrone.

17-METHYL OR 17-ETHYNYL-SIDE-CHAINS TEND TO INCREASE THE ORAL ACTIVITY of compounds which are otherwise comparatively inactive by this route. Thus methyl-testosterone, ethynyl-estradiol and ethynyl-testosterone are more active when taken by mouth than estradiol or testosterone. However, such a side-chain may cause a qualitative change in the pharmacologic properties as shown by the fact that unlike testosterone, ethynyl-testosterone exhibits intense luteoid, but only slight testoid properties.

ESTERIFICATION CAUSES NO QUALITATIVE CHANGE IN ACTIVITY but may either increase or decrease the potency of a steroid It usually acts by changing the rate of absorption, utilization or elimination of the free compound. In the case of most hormonal activities, potency is increased if esterification leads to an appropriate delay in the absorption rate and vice versa. Conversely, the anesthetic effect is most readily obtained if the organism is suddenly flooded with the compound. As regards the testoid effect of testosterone, enol-esters proved less potent, the corresponding hydroxy-esters more potent than the free compound.

OXIDATION AT BOTH EXTREME POLES OF THE MOLECULE APPEARS TO BE ADVANTAGEOUS FOR ALL BIOLOGIC ACTIVITIES (C_3 and C_{17} among the estranes and androstanes and C_3 and $C_{17}{}^1$ or $C_{17}{}^2$ among the C_{17} alkyl substituted androstanes).

In general it may be said that, judged by the evidence available at this time,

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AN α,β UNSATURATED KETONE GROUP AT C_3 is not essential for corticoid activity since both pregnenolone and acetoxy pregnenolone proved to possess *this property*. Even completely saturated compounds (dihydro-corticosterone, that is 17(β)-[1-keto-2-hydroxyethyl]-*androstane*-3-one-11(β)-ol) may exhibit slight corticoid activity of the pro-muscular efficiency type. However, the α,β unsaturated ketone group is apparently advantageous since all the most active corticoids possess it.

A HYDROXYL, OR ACETOXY GROUP AT C_{17}[2] is beneficial as shown by the fact that desoxycorticosterone and its acetate are more potent than progesterone *and acetoxy pregnenolone is more potent* than pregnenolone.

OXYGEN AT C_{11} in the form of a hydroxyl or ketone, proved indispensable for the gluco-corticoid and the pro-muscular efficiency activity of all steroids so far examined. Its importance is best shown by comparing corticosterone with desoxycorticosterone, since the latter differs from the former only in that it is deprived of the alcoholic oxygen at C_{11}. This loss leads to the disappearance of gluco-corticoid activity in desoxycorticosterone although the compound is highly active with *regard to* the life-maintaining and mineralo-corticoid effects.

The luteoids. — Only androstane derivatives possess luteoid activity but the possession of a C_{17} SIDE-CHAIN, though very beneficial, is not indispensable since testosterone *and Δ^4-androstene*-3,17-dione proved effective.

AN α,β UNSATURATED KETONE GROUP AT C_3 is advantageous and present in all of the most active luteoids (progesterone, ethynyl-testosterone). Yet it is not essential since 17(β)-ethyl-*androstane-3-one-17(α)-ol* and 17(α)-ethyl-*androstane*-3(β)-17(α)-diol both proved effective.

SHIFT OF THE DOUBLE BOND from Δ^4 to Δ^5 (Δ^5-iso-progesterone) greatly diminishes or destroys luteoid potency. The addition to the Δ^4 of a Δ^6-double bond as in 6-dehydro-progesterone, or a Δ^{11} double bond as in 11-dehydro-progesterone, cause only a slight decrease in potency. On the other hand an additional Δ^{16} double bond as in 16-*dehydro-progesterone results in complete* inactivation.

ANY DEVIATION FROM THE PROGESTERONE STRUCTURE decreases activity. 3-desoxy-progesterone proved inactive in the doses tested. Reduction of the C_{17}[1]-ketone to a hydroxyl group likewise destroys activity. Addition of a $C_6(\alpha)$ or C_{12} hydroxyl decreases but does not destroy luteoid potency. The *same is true of the introduction of a* 6-keto group. Addition of a C_{11} or C_{17}-hydroxyl is claimed to destroy luteoid activity completely.

The testoids.— A C_{17} SIDE-CHAIN is usually detrimental, but under certain conditions methyl-testosterone proved *actually more active than testosterone:* even ethyl-testosterone and ethynyl-testosterone — though less active than testosterone — possess marked testoid potency. The oral activity of androstanes improves by C_{17}-alkyl substitution. Methyl-testosterone is partic*ularly active by mouth. Among* C_{17}-ethyl substituted androstanes the pro-prostatic effect is more common than the seminal vesicle stimulating potency This is quite obvious in progesterone, pregnenolone and Kendall's Compound "E", that is 17(β)-[1-keto-2-hydroxy-ethyl]-Δ^4-*androstene*-3,11-dione-17(α)-ol.

UNSATURATION is not of great importance for testoid activity, one of the most potent naturally occurring testoids (androsterone) is fully saturated. A shift of the double bond from Δ^4, as in testosterone, to another position diminishes, but does not abolish activity as shown by the fact that the double bond isomerides Δ^1-iso-testosterone (Δ^1-*androstene-3-one-17(α)-ol) and* Δ^5-iso-

testosterone are both endowed with some testoid activity. It is also true that if an additional double bond is introduced into testosterone, as in $\Delta^{4,6}$-*androstadiene*-3-one-17(α)-ol, activity diminishes without disappearing.

A SINGLE OXYGEN suffices to endow androstane with some testoid activity, as shown by the fact that the 17-amine of androstane-3-ol and the 3-chloro derivative of androstane-17-one are both slightly active, as is Δ^5-*androstene*-3(β)-ol. The completely reduced parent hydrocarbon, androstane, has not been assayed as yet. Introduction of MORE THAN THE USUAL TWO OXYGENS decreases activity, but adrenosterone (Δ^4-*androstene*-3,11,17-trione) still possesses about one-fifth the potency of androsterone and *androstane*-3,17-dione-11-ol as well as *androstane*-3(β)-11-diol-17-*one* are highly testoid.

The presence at C_3 and C_{17} of either ALCOHOLIC OR KETONIC OXYGEN is compatible with a high degree of testoid potency. Indeed, all not-alkyl-substituted androstanes or androstenes containing only 2 (alcoholic or ketonic) oxygens, one at C_3 and one at C_{17}, possess some testoid activity.

THE STERIC POSITION OF THE C_3 AND C_{17} HYDROXYLS plays a very important rôle in determining the degree of testoid potency. In the great majority of the compounds investigated, the alpha position is preferable at both these locations.

A 17^2-ACETOXY GROUP is definitely detrimental inasmuch as both desoxycorticosterone acetate and acetoxy-pregnenolone fail to exhibit the pro-prostatic effect which is so clear in the case of progesterone and pregnenolone. It will be remembered that the former two compounds differ from the latter two, only in that they have an additional 17^2-acetoxy group. The free 17^2-hydroxy compounds have not been adequately tested as yet, but presumably they act in essentially the same manner as the acetylated alcohols.

The spermatogenic steroids. — A C_{17} SIDE-CHAIN is not essential, indeed not even of much consequence for this effect, since one of the most active compounds proved to be androstenediol, the other pregnenolone.

Completely SATURATED COMPOUNDS (androsterone), as well as Δ^4- (testosterone, progesterone) or Δ^5-unsaturated steroids (androstenediol, pregnenolone) were found to possess a high degree of spermatogenic activity.

The addition of an ACETOXY GROUP AT $C_{17}{}^2$ completely destroys spermatogenic activity in progesterone and pregnenolone as shown by the inactivity of desoxycorticosterone and acetoxy-pregnenolone.

The anesthetic steroids. — EVEN ETIOCHOLANE DERIVATIVES possess this effect.

A C_{17} SIDE-CHAIN is beneficial, but not indispensable as shown by the fact that 17-ethyl substituted etiocholanes and androstanes are among the most active anesthetics, yet etiocholanes and androstanes, which are not alkyl substituted, also proved highly active.

One DOUBLE BOND, if it is situated in ring A or B, does not appear to interfere seriously with the anesthetic effect but 2 or more double bonds in these 2 rings or 1 double bond in ring D are detrimental.

The highest anesthetic effect is exhibited by STEROIDS OXYGENATED ONLY AT THE TWO EXTREME ENDS OF THE MOLECULE.

The STERIC POSITION OF THE HYDROXYL GROUP IN POSITION C_3 appears to be without importance for the anesthetic effect as shown by the observation that the two isomeric androsterones are of equal activity, as are the two isomeric *etiocholane*-3-ol-17-ones.

A 5-MEMBERED RING D is not indispensable for the anesthetic effect as shown by the high activity of D-homo-androstane derivatives.

GENERAL RULES REGULATING THE ACTIONS OF STEROID HORMONES

Compensatory Atrophy. — As with most other hormonal compounds, exogenous administration of steroid hormones causes compensatory atrophy of the cells normally concerned with their elaboration. This is a useful compensatory arrangement, since in the presence of excessive exogenous quantities of a certain hormone, there is no need for its production by the organism. In this compensation it is the pharmacologic activity which counts and not the chemical structure of the compound Thus ovarian atrophy is also produced by stilbene derivatives, which bear no close chemical relationship to the folliculoids and Leydig cell atrophy is induced by synthetic testoids (e.g., methyl-testosterone), which normally neither occur nor give rise to physiologic testoid metabolites in the body.

It is customary to distinguish between SIMPLE AND TRANSFERRED COMPENSATORY ATROPHY A compensatory atrophy is simple when it affects the cell *type which normally elaborates the hormone* administered. It is transferred, when it affects a cell type which normally does not produce the hormone given, but one having similar pharmacologic properties. Thus, for instance, the Leydig cell atrophy produced by testosterone is a simple compensatory atrophy, because the Leydig cells normally elaborate this substance. On the other hand, the Leydig cell atrophy produced by stilbestrol represents an example of transferred compensatory atrophy.

It is noteworthy that the compensatory atrophy of an endocrine cell, which normally produces several pharmacologically different hormones, often interferes not only with the secretion of the hormone given but also with that of these other, pharmacologically different, steroids This is also a type of transferred compensatory atrophy. Thus, involution of the adrenal-cortical cells, due to desoxycorticosterone treatment, interferes not only with the secretion of mineralo-corticoids, such as desoxycorticosterone itself, but also with that of gluco-corticoids of the corticosterone type. *This may explain the singular* phenomenon that animals overdosed with desoxycorticosterone may exhibit signs of cortical deficiency (in*asmuch as they have a great tendency* to develop hypoglycemia), perhaps because of subnormal gluco-corticoid production.

It will be kept in mind that the terms simple and transferred compensatory atrophy bear no relation to the designations "direct" and "mediated" (or indirect) hormone actions. Compensatory atrophy may — as so many hormone actions — be due to the immediate, direct effect of a hormone upon the target organ or it may be mediated through another gland (e.g., the hypophysis).

Adaptation. — There is no clear-cut evidence, as yet, to prove that treatment with steroid hormones of any kind *gives rise to the formation of true anti*hormones. However, following prolonged pretreatment with a steroid hormone, some kind of adaptation to it may occur. Thus, during chronic treatment with estradiol, the adrenal cortex at first undergoes marked hypertrophy and *the body weight declines. Later, however, both the adrenal size and the body* weight revert towards normal in spite of continued treatment This is not an immunity to estradiol, as such, since animals pretreated with this compound become comparatively resistant, not only to this hormone, but also to the chemically unrelated stilbestrol.

Similarly, chronic treatment with anesthetic doses of steroid compounds produces resistance not only to the narcotic effect of the steroid with which pretreatment occurred, but also to that of other steroids. These observations clearly indicate that adaptation may occur, not only to chemical substances,

but also to certain pharmacologic actions

Dissociated Adaptation. — It has been found that following treatment with steroid compounds, the organism may become selectively resistant to some of their actions, without acquiring insensivity to others. This is termed "dissociated adaptation."

Thus, following repeated intraperitoneal injections of certain steroids, rats can acquire resistance to the anesthetic effect of these compounds without becoming insensitive to their hormonal actions. Similarly, rats chronically treated with desoxycorticosterone may become resistant to some properties of this compound (involution of the thymico-lymphatic apparatus) although the treatment continues to cause compensatory atrophy of the adrenals, hypochloremia, etc. Such examples of selective acquired resistance give additional support to the concept that adaptation to steroid hormones is not due to antihormone formation, since antihormones nullify all the actions of the corresponding hormones.

Inverse Response. — Depending upon circumstances, the same steroid hormone may exhibit two diametrically opposed pharmacologic actions. Observations which illustrate this fact have already been cited above, in other connections. Thus, we said that small doses of folliculoids enhance, while large doses inhibit the effects of luteoids We have also seen that small doses of testosterone cause atrophy of the seminiferous epithelium, while large doses protect the spermatogenic elements against atrophy. The mechanism of this inverse response is not yet fully understood and it is rather probable that its cause is not the same in every instance.

Direct and Mediated Actions. — Some of the pharmacologic actions of steroids are apparently DIRECT. Thus, the effect of estradiol upon the vaginal epithelium or the endometrium appears to be due to the direct action of this hormone upon the responsive cells, since it is most readily elicited by local application of the hormone. Similar experiments have proven the direct effect of progesterone upon the endometrium and of testosterone upon the capon's comb.

Other actions are MEDIATED OR INDIRECT. Thus, large doses of folliculoids cause corpus luteum formation and progestational proliferation of the endometrium in intact females. These actions are apparently mediated through the anterior lobe of the pituitary whose gonadotrophic hormone and prolactin production is increased by them This results in the formation of large, "pregnancy type" corpora lutea which in turn affect the endometrium through excessive secretion of progesterone. Here we have a clear-cut example of the indirect actions which are dependent, in the case of the ovarian response, upon one (hypophysis) and in the case of the endometrial reaction, upon two (hypophysis and ovary) intermediate stations, whose integrity is essential for the response

Another type of mediated action is that which depends, not upon the stimulation of the hormone formation in an intermediate organ, but upon transformation in the body of an inactive into an active steroid. Thus certain folliculoid hormones are ineffective when directly applied to the vaginal epithelium in comparatively high doses, yet when injected subcutaneously, they cause vaginal cornification at dosage levels which could not give rise to a similar concentration in the vagina. Here, we must assume that it is within the organism that the injected steroid is transformed into an active folliculoid.

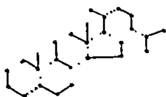
BIOGENESIS AND METABOLISM OF THE STEROIDS

It is obviously of the greatest importance to determine the manner in which the body forms the steroid hormones

(biogenesis) and the mechanism through which these are eventually destroyed or eliminated (metabolism).

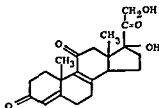
Biogenesis. — There are two principal schools of thought concerning the mechanism through which the body makes steroid hormones. Some investigators believe that these are synthetized directly from smaller molecules, while others consider it more probable that they are formed from cholesterol by degradation of the side chain.

Reichstein expressed the view that the isolation of the numerous highly oxidized adrenal-cortical steroids — many of which still contain actual sugar remnants in their molecule — make the former hypothesis more likely. He considers it possible that the adrenal steroids are FORMED FROM SUGARS and are progressively reduced to cholesterol-like compounds. In this connection he emphasized that not only the hormones of the 21 carbon atom series, but numerous other physiologically important steroids, such as cholesterol and the bile acids, contain a skeleton in which the number of carbon atoms is divisible by 3 and could theoretically be reconstructed from three or six carbon-atom chains, such as are typical of sugars (e.g., dihydroxy-acetone, glyceric aldehyde). This is illustrated by the following formula :



Rittenberg described experiments on mice in which a constant deuterium content of *1.5 atom percent* was maintained. After 60 days the cholesterol in the body of these mice showed a relation between deuterium and hydrogen content which was half that found in body fluids. It was concluded that at least 22 H atoms of cholesterol are exchangeable with the deuterium of the body fluids in some step of its biogenesis. This fact was interpreted to mean that cholesterol is SYNTHETIZED IN THE BODY FROM SMALLER MOLECULES. Furthermore, deuterium has been found in pregnanediol, isolated from the urine of a woman to whom deutero-cholesterol had been administered (*Bloch*). Apparently, ½ to ⅔ of the pregnanediol excreted arose by degradation of this cholesterol. The possibility of hydrogen-deuterium exchange reactions has been eliminated, since the amount of deuterium present in the cholesterol and pregnanediol thus formed, is greater than could thus be accounted for. All these findings suggest that cholesterol is first built up from one, two or three carbon compounds and subsequently, degraded to the steroid hormones. In the body, these reactions do not proceed automatically, however, since otherwise, an increased intake of such 1-3 carbon compounds, or of cholesterol, would necessarily lead to an increased steroid hormone production. Probably, the gonado- and adrenotrophic hormones play an important rôle in determining not only the total amount, but also the type of the steroid hormones produced from whatever their precursor may be.

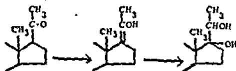
Marker suggested that at least all cortical steroids may be FORMED BY REDUCTION OF A HITHERTO NOT YET ISOLATED HYPOTHETIC PARENT COMPOUND :



This highly oxygenated steroid "may be the as yet unisolated cortical hormone" However, this theory is not supported by any established fact.

Marrian expressed a somewhat different view and suggested that the STEROIDS WITH C_{17} TERTIARY HYDROXYLS

ARE SECONDARILY FORMED BY THE ADDITION OF H_2O TO THE DOUBLE BOND OF AN ENOLIZED $C_{17}{}^1$ KETO-STEROID in the following manner :



If Marrian's theory of C_{17} side-chain oxidation is correct, corticoids could be formed from progesterone and testoid androstanes could arise from 17-ethyl-androstanes, by oxidation between C_{17} and $C_{17}{}^1$ which could lead to C_{17} oxygenated androstane derivatives.

Several investigators speculated upon the POSSIBLE INTERCONVERSIONS OF STEROID HORMONES WITHIN THE BODY. In the chart below we summarized what we consider a possible route for the biogenesis of the different types of hormonal compounds, assuming that they originate from pregnenolone which in turn may arise either from cholesterol by degradation of the side-chain, or by direct synthesis from smaller molecules. It was felt that such a synopsis would help to visualize the possible hormone interconversions which may take place within the organism, as well as the form in which the hormones can be recovered from urine. It must be admitted that many steps indicated in the table rest on insufficient evidence. However, some of these interconversions have definitely been proven by injecting a certain chemical compound and recovering its metabolites from the urine. Only those urinary steroids are listed which were actually isolated from normal human urine and are presumably of major importance. These observations proved beyond doubt the pharmacologically most important fact, that the biologic results elicited by a certain compound are not necessarily caused by this compound, as such, but may be due to other steroids formed within the body from the injected compound.

A study of the chart shows the prominent rôle played by pregnenolone. If the hormones are derived from cholesterol this compound would appear to be the logical parent substance of all steroid hormones, as it differs from cholesterol only in the side-chain. Pharmacologically, pregnenolone also occupies a rather unique position as it is the only compound known to possess all the independent steroid hormone actions. (The testoid action is somewhat doubtful as pregnenolone stimulates only the prostate in castrate rats.) It appears that the specialization for a certain pharmacologic action occurs gradually and always at the expense of other activities which are present — even if only to a slight degree — in the parent compound. This differentiation is rather reminiscent of the evolution of highly specialized cells from "multi-potent" but undifferentiated embryonic cells.

It will be noted that the direction of the conversions which occur in the body obviously cannot be merely automatic. If this were the case, pregnenolone — or any other steroid which would prove to be the hypothetical parent substance — would always give rise to the same hormone combination. This would not allow for the hormonal differences between male and female organisms and the qualitative changes in the type of hormone production during the various phases of the estrous cycle, pregnancy, adaptation to changes in environment, etc. It is highly probable that the power to direct such interconversions is within the steroid hormone producing endocrine cells, which in turn are mainly under pituitary control. Conversely, through hormonal mechanisms, such as those responsible for compensatory hypertrophy or atrophy, the steroid-producing cells can act back on the pituitary, thus regulating its "trophic" hormone production.

Many puzzling pharmacologic problems may perhaps be solved by the elucidation of these hormone interconver-

Possible Biogenesis of the Steroid Hormones from Pregnenolone

17-KS (NEUTRAL, NON-PHENOLIC)

17-KS (ACID, PHENOLIC)

sions in the body. Thus there is a surprising difference in the folliculoid action of saturated and unsaturated androstane derivatives. Compounds having a double bond in rings A or B tend to exhibit a marked pro-vaginal cornification effect, while little or no such potency could be detected in saturated androstanes. This may mean that the folliculoid activity of androstenes is, at least partly, due to conversion into the highly unsaturated estratrienes

Metabolic factors influencing the activity of the steroids. — *It is not within the scope of this book to discuss, in detail, the extensive literature concerning the metabolism of steroids. The many species differences in the manner in which the body handles these compounds, the isolation from urine, or tissues, of incompletely identified steroids, etc., are of interest only to the specialist. Hence, we shall limit ourselves to a brief survey of the salient metabolic factors which are likely to influence the activity of the steroids.*

In general, enterally or parenterally given steroids are well ABSORBED. *Unlike the protein hormones, they are not readily destroyed by the gastrointestinal juices, and unlike for cholesterol, bile is not essential for the intestinal absorption of the steroids. That most steroids are comparatively inactive when given by mouth is not due to destruction in the intestine or slow absorption but, on the contrary, to unduly rapid absorption and consequent speedy destruction and excretion (in urine and bile) before their full effect could take place. To some extent the relative inefficiency of orally administered steroids is also due to the circumstance, that they are directly led to the liver through the portal vein.*

The LIVER *plays an important rôle in the detoxification of all steroid hormones. After partial hepatectomy both the hormonal and the anesthetic effects of steroids are greatly increased. Furthermore, subcutaneous implantation of hormone pellets is more effective than intra-splenic implantation, presumably because in the latter case all the absorbed material is immediately exposed to the detoxifying hepatic cells as it passes through the portal circulation. We do not know as yet what chemical factors are responsible for this action of the liver, but judged by in vitro experiments on the inactivation of estratrienes by liver slices, it is highly probable that enzymes play an important part. The detoxification may be achieved by degradation to inactive compounds or by conjugation, which make the steroids less active or increase the rate of their elimination.*

In the case of desoxycorticosterone acetate and progesterone, HYPOPHYSECTOMY *or* ADRENALECTOMY *increases the animal's sensitivity towards the anesthetic effect, while no such increase is obtained by* NEPHRECTOMY *or* THYROIDECTOMY. *Apparently the hypophysis and the adrenal also play an important part in the detoxification of the steroids and perhaps these glands exert their effect partly through their action upon the hepatic cells.*

The general depression of metabolism caused by thyroidectomy and the interference with renal elimination occasioned by nephrectomy on the other hand, cause no important change in the sensitivity of the organism to steroids. It must be kept in mind that probably a large part of the excreted steroid hormone degradation products and conjugated steroids are inactivated even before they are excreted.

Hypophysectomy may even cause a qualitative change in the response to certain steroids as shown by the example of testosterone which normally causes mucification but after hypophysectomy induces persistent cornification of the rat vagina. It remains to be seen whether the folliculoid activity assumed by the compound after hypophysectomy is due to an improvement in its transformation into an active estratriene, or whether removal of the pituitary merely inhibits those actions of the testosterone molecule which normally "mask" its own folliculoid properties.

The above-mentioned examples clearly demonstrate that factors within the organism are of the greatest importance in determining the pharmacologic response to a steroid compound.

I Steroids isolated from the adrenal *

Systematic name in terminology of this book	*Other names*
$\Delta^{1,3,5,10}$-*estratriene*-3-ol-17-one	Estrone
androstane-3(β),11(β)-diol-17-one	Reichstein's mono-ketone m.p.: 236°
Δ^{4}-*androstene*-3,17-dione	———
Δ^{4}-*androstene*-3,11,17-trione	Adrenosterone
17(β)-[1-ketoethyl]-*androstane*-3(β)-ol	Allopregnanolone
17(β)-[1(α)-hydroxyethyl]-*androstane*-3(β), 17(α)-diol	Reichstein's cpd. "O"
17(β)-[1(β)-hydroxyethyl]-*androstane*-3(β),17(α)-diol	Reichstein's cpd. "J"
17(β)-[1-ketoethyl]-*androstane*-3(β), 17(α)-diol	Reichstein's cpd. "L"; Wintersteiner's cpd. "G".
17(β)-[1(β),2-dihydroxyethyl]-*androstane*-3(β),17(α)-diol	Reichstein's cpd. "K".
17(β)-[1-keto-2-hydroxyethyl]-*androstane*-3(β), 11(?)-diol	Reichstein's cpd "R".
17(β)-[1-keto-2-hydroxyethyl]-*androstane*-3(β),17(α)-diol	Reichstein's cpd. "P".
17(β)-[1-keto-2-hydroxyethyl]-*androstane*-3(β)-ol-11-one	Reichstein's cpd. "N"; Kendall's cpd. "H".
17(β)-[1(?),2-dihydroxyethyl]-*androstane*-3(β),11(β),17(α)-triol	Reichstein's cpd. "A"; Kendall's cpd. "D"; Winter-teiner's cpd. "A".
17(β)-[1-keto-2-hydroxyethyl]-*androstane*-3(α),11(?),17(α)-triol	Reichstein's cpd. "C"; Kendall's cpd. "C"; Wintersteiner's cpd. "D".

* Continued on next page

Systematic name in terminology of this book	*Other names*
17(β)-[1-keto-2-hydroxyethyl]-*androstane*-3(β),11(β),17(α)-triol	Reichstein's cpd. "V".
17(β)-[1-keto-2-hydroxyethyl]-*androstane*-3(β),17(α)-diol-11-one	Reichstein's cpd. "D"; Kendall's cpd. "G"; Wintersteiner's cpd. "B".
17(β)-[1-ketoethyl]-Δ^4-*androstene*-3-one	Progesterone
17(β)-[1-ketoethyl]-Δ^4-*androstene*-3-one-17(α)-ol	17(β)-hydroxy-progesterone
17(β)-[1-keto-2-hydroxyethyl]-Δ^4-*androstene*-3-one	Desoxycorticosterone; Reichstein's cpd. "Q"; Kendall's desoxy cpd. "B".
17(β)-[1(?),2-dihydroxyethyl]-Δ^4-*androstene*-3,11-dione	Reichstein's cpd. "T".
17(β)-[1-keto-2-hydroxyethyl]-Δ^4-*androstene*-3-one-11(β)-ol	Corticosterone; Reichstein's cpd. "H"; Kendall's cpd. "B"
17(β)-[1-keto-2-hydroxyethyl]-Δ^4-*androstene*-3-one-17(α)-ol	Reichstein's cpd. "S".
17(β)-[1-keto-2-hydroxyethyl]-Δ^4-*androstene*-3,11-dione	Dehydro-corticosterone; Kendall's cpd. "A".
, β-Unsaturated ketone ($C_{21}H_{28-30}O_4$) constitution unknown	————
17(β)-[1(?),2-dihydroxyethyl]-Δ^4-*androstene*-3-one-11(β),17(α)-diol	Reichstein's cpd. "E".
17(β)-[1-keto-2-hydroxyethyl]-Δ^4-*androstene*-3-one-11(β),17(α)-diol	17-hydroxy-corticosterone; Reichstein's cpd. "M"; Kenall's cpd. "F".
17(β)-[1(?),2-dihydroxyethyl]-Δ^4-*androstene*-3,11-dione-17(α)-ol	Reichstein's cpd. "U".
17(β)-[1-keto-2-hydroxyethyl]-Δ^4-*androstene*-3,11-dione-17(α)-ol	Reichstein's cpd. "Fa"; Kendall's cpd. "E"; Wintersteiner's cpd. "F"; 17-hydroxy-dehydrocorticosterone.

Note that the configuration of the 17-hydroxyls is designated contrary to *hitherto accepted convention* which described them as "β".

I. Steroids isolated from the adrenal *

Systematic name in terminology of this book	*Other names*
$\Delta^{1,3,5,10}$-*estratriene*-3-ol-17-one	Estrone
androstane-3(β),11 (β)-diol-17-one	Reichstein's mono-ketone m.p., 236°
Δ^{4}-*androstene*-3,17-dione	———
Δ^{4}-*androstene*-3,11,17-trione	Adrenosterone
17(β)-[1-ketoethyl]-*androstane*-3(β)-ol	Allopregnanolone
17(β)-[1(α)-hydroxyethyl]-*androstane*-3(β), 17(α)-diol	Reichstein's cpd. "O"
17(β)-[1(β)-hydroxyethyl]-*androstane*-3(β),17(α)-diol	Reichstein's cpd. "J"
17(β)-[1-ketoethyl]-*androstane*-3(β), 17(α)-diol	Reichstein's cpd. "L"; Wintersteiner's cpd. "G".
17(β)-[1(β),2-dihydroxyethyl]-*androstane*-3(β),17(α)-diol	Reichstein's cpd. "K".
17(β)-[1-keto-2-hydroxyethyl]-*androstane*-3(β), 11(?)-diol	Reichstein's cpd. "R".
17(β)-[1-keto-2-hydroxyethyl]-*androstane*-3(β),17(α)-diol	Reichstein's cpd. "P".
17(β)-[1-keto-2-hydroxyethyl]-*androstane*-3(β)-ol-11-one	Reichstein's cpd. "N"; Kendall's cpd. "H".
17(β)-[1(?),2-dihydroxyethyl]-*androstane*-3(β),11(β),17(α)-triol	Reichstein's cpd. "A"; Kendall's cpd. "D"; Wintersteiner's cpd. "A".
17(β)-[1-keto-2-hydroxyethyl]-*androstane*-3(α),11(?),17(α)-triol	Reichstein's cpd. "C"; Kendall's cpd. "C"; Wintersteiner's cpd. "D".

* Continued on next page

Systematic name in terminology of this book	*Other names*	*Sources*
Δ^{11}-*androstene*-3(α)-ol-17-one	——	Man ♀ with adrenal tumor
Δ^{5}-*androstene*-3(β),16(β),17(β)-triol	——	*Man with adrenal carcinoma*
$\Delta^{3,5}$-*androstadiene*-17-one	——	Man ♂, ♀, ♂ and ♀ with adrenal tumor, (Artefact?)
17(β)-[1(α)-hydroxyethyl]-*androstane*-3(α)-ol	Epi-allo-pregnane-diol, Allo-pregnane-3(α),20(α)-diol	*Man ♀, cattle ♂; pregnant: woman,* cow, mare
ndrostane-3(β)-ol	Allo-pregnane-3(β),20(β)-diol	Cattle ♂; pregnant: woman, cow, mare
ndrostane-3(β)-ol	Allo-pregnane-3(β),20(β)-diol	Pregnant mare
ne-3(α)-ol	Epi-allo-pregnanolone	Pregnant woman
ne-3(β)-ol	Allo-pregnanolone	Pregnant: woman, sow, mare
ne-3-one	Allo-pregnanedione	Pregnant mare
ndrostane-3(α),16(?)-diol	Pregnanetriol "B"	Pregnant mare
]-*androstane*-3(β),11(?)-diol	Allo-pregnane-3(β),11,20,21-tetrol	Horse ♂
	——	Man ♂
	Etiocholanolone	Man ♀, ♀/c, ♂/c, ♀ with adrenal tumor, ♀ with breast cancer
e	11-keto-etiocholanolone	Man ♂, adrenal carcinoma
l	Epi-pregnanol-3	*Pregnant: woman*
ocholane-3(α)-ol	Pregnanediol	Pregnant: woman, chimpanzee, mare, cow
iocholane-3(α)-ol-Na. glucuronidate	Pregnanediol as Na. glucuronidate	Man ♀, ♀/c, ♂; cattle ♂
ne-3(α)-ol	Epi-pregnanolone	Pregnant: woman, sow
ne-3-one	Pregnanedione	Pregnant mare
iocholane-3(α),17(α)-diol	Pregnanetriol	Man ♀, ♀ with adrenal tumor
17(β)-ethyl-9-*epietiocholane*-3(β),11(?)-diol	Urane-3(β),11( )-diol	Pregnant mare (structure uncertain)
17(β)-ethyl-9-*epietiocholane*-3-one-11(?)-ol	Urane-3-one-11( )-ol	Pregnant mare (structure uncertain)
17(β)-[1(α)-hydroxyethyl]-9-*epietiocholane*-3(α), 11(β)-diol	Urane-3(α),11(β),20(α)-triol; Pregnanetriol "A"	Stallion; Pregnant: woman, mare (structure uncertain)
Structure unknown	Active urinary corticoid	Man ♂, ♀, adrenal tumor, alarm reaction

II. Steroids isolated from urine *

Systematic name in terminology of this book	*Other names*	*Sources*
Estrane-3(?),17(α)-diol	Octahydro-estrone; Estranediol B	Man ♀
Estrane-3(?),17(?)-diol	Estranediol A	Man ♀
$\Delta^{1,3,5,10}$-*estratriene*-3-17(α)-diol	α-estradiol	Pregnant: woman, mare
$\Delta^{1,3,5,10}$-*estratriene*-3,17(β)-diol	β-estradiol	Pregnant mare
$\Delta^{1,3,5,10}$ *estratriene*-3-ol-17-one	Estrone	Man ♂ stallion, cattle ♂; pregnant. woman, mare
$\Delta^{1,3,5,10}$-*estratriene*-3-ol-17-one-Na. sulphate	Estrone as Na. sulphate	Pregnant mare
$\Delta^{1,3,5,10}$-*estratriene*-3,16(β),17(α)-triol	Estriol	Pregnant woman
$\Delta^{1,3,5,10}$ *estratriene*-3,16(β),17(α)-triol-Na glucuronidate	Estriol as Na. glucuronidate	Pregnant woman
$\Delta^{5,10,6,8}$-*estratriene*-3(β)-ol-17-one	———	Pregnant mare
$\Delta^{1,3,5,10,7}$-*estratetraene*-3-ol-17-one	Equilin	Pregnant mare
An isomer of above	Hippulin	Pregnant mare
$\Delta^{1,3,5,10,6,8}$-*estrapentaene*-3,17(β)-diol	17β-dihydro-equilenin	Pregnant mare
$\Delta^{1,3,5,10,6,8}$-*estrapentaene*-3-ol-17-one	Equilenin	Pregnant mare
$\Delta^{1,3,5,10,6,8}$-*estrapentaene*-11,17-dione	3-desoxy-11-keto-equilenin	Pregnant mare
Androstane-3(α),17(α)-diol	———	Man ♂
Androstane-3(β)-ol-x-one	———	Pregnant mare
Androstane-3(α)-ol-17-one	Androsterone, cis-androsterone	Man ♂, ♂/c, ♀, ♀/c with adrenal tumor; cattle ♂; pregnant: woman, cow
Androstane-3(α)-ol-17-one-Na. sulphate	Androsterone as Na. Sulphate	Man ♂ with leydig cell tumor
Androstane-3(β)-ol-17-one	Iso-androsterone, trans-androsterone	Man ♀, ♀ with adrenal hyperplasia; ♀ with ovarian cysts, ♂ with cancer
Androstane-3,17-dione	Androstanedione	Man ♂, ♀ with adrenal carcinoma
Androstane-3(α)11(β)-diol-17-one	11-hydroxy-androsterone	Man ♂, adrenal carcinoma
$\Delta^{2?}$-*androstene*-17-one	$\Delta^{2?}$-androsterone	Man: ♂, ♂ with cancer, ♀/c, (Artefact?)
Δ^{5}-*androstene*-3(β)-ol-17-one	Dehydro-iso-androsterone	Man ♂, ♂/c, ♀, ♀/c, ♀ with adrenal tumor; cattle ♂; pregnant: cow

* Continued on next page

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DODDS, E. C.: *Possibilities in the Realm of Synthetic Estrogens* Vitamins and Hormones. Advances in research and applications Ed. by R. S Harris and K. V. Thimann 3, 229 (1945). Academic Press Inc. Publ. New York (1945).

A very brief (6 pages), but most authoritative and stimulating summary, of problems in the field of artificial folliculoids.

FIESER, L. F.: *The Chemistry of Natural Products Related to Phenanthrene* Reinhold Publishing Corporation. New York, U S.A. (1936)

This volume (358 pages) deals with the chemistry of all phenanthrene derivatives from the chemical point of view; only occasional annotations concerning biologic activity are included. The volume is very authoritative, but outdated

MASSON, GEORGES: *Les Hormones artificielles.* Rev Canad. de Biol. 3, 491 (1944).

A detailed (90 pages) review concerning the artificial folliculoids and their derivatives It lists the principal chemical and pharmacologic properties of these compounds and gives a brief synopsis of pertinent bioassay methods as well as of the pharmaco-chemical correlations within this group *It is useful* mainly to research workers who specialize in this field. (In French.)

PINCUS, GREGORY AND WILLIAM H. PEARLMAN: *The Intermediate Metabolism of the Sex Hormones.* Vitamins and Hormones Advances in Research and Applications Ed by R. S Harris and K. V. Thimann. 1, 294 (1943) Academic Press Inc Publ, New York (1943)

Very authoritative review (47 pages, 244 references), concerning the biogenesis and metabolism of folliculoid and testoid hormones Numerous synoptic tables and charts help to illustrate this very readable and instructive article It does not attempt to survey the pertinent literature completely

REICHSTEIN, T AND C W SHOPPEE: *The Hormones of the Adrenal Cortex* Vitamins and Hormones Advances in Research and Applications. Ed. by R S Harris and K. V Thimann. 1, 346 (1943) Academic Press Inc Publ New York (1943)

A rather detailed masterly review (52 pages, 207 references) A brief introductory section deals with the biologic importance and bioassay of the corticoids, but most of the text is devoted to the isolation, structure and partial synthesis of the corticoids and their derivatives

SELYE, HANS: *The pharmacology of Steroid Hormones and their Derivatives.* Rev. Canad. de Biol. 1, 577 (1942).

Fairly extensive review concerning the pharmacology of the steroid hormones and their derivatives, with a brief section which deals with their metabolism.

SELYE, HANS *Encyclopedia of Endocrinology, Section I. Classified Index of Steroid Hormones and Related Compounds.* Vol. 1-4. A.W.T Franks, Publ, Montreal (1943)

An index listing the main chemical and pharmacologic properties of the steroid hormones and their derivatives. The volumes are presented in loose-leaf form, a separate page being assigned to each of the (more than 700) parent compounds. — The introductory section gives a concise description of the chemical and pharmacologic nomenclature and system of classification. An appendix contains synoptic charts (which list the steroids naturally occurring in various biologic materials), a dictionary of bioassay technics etc These volumes are useful only to research workers, specializing in the steroid hormone field.

SOBOTKA, HARRY *The Chemistry of the Steroids.* The Williams & Wilkins Company, Baltimore (1938).

An extensive (634 pages) treatise describing the principal chemical properties of the steroids This interesting volume is most useful to those interested in steroid chemistry, but is somewhat out of date.

STRAIN, WILLIAM H: *Chapter 19. The Steroids* Organic Chemistry. An Advanced Treatise Ed. by Henry Gilman 2, 1341 (1943) 2nd Ed. John Wiley & Sons, Inc. Publ New York, (1943)

A large (190 pages) and excellently written chapter which deals with the chemistry of the steroids This is undoubtedly one of the best, comparatively up-to-date, descriptions of this field It is most useful to those interested in the purely chemical aspects of the subject and does not attempt to discuss biologic and pharmacologic problems.

III. Steroids isolated from the testis

Systematic name in terminology of this book	*Other names*
$\Delta^{1,3,5,10}$-*estratriene*-3,17(α)-diol	α-estradiol
$\Delta^{1,3,5,10}$-*estratriene*-3-ol-17-one	Estrone
Androstane-3,17-dione	———
Δ^{4}-*androstene*-3-one-17(α)-ol	Testosterone
Steroid of unknown structure $C_{21}H_{32}O_3$	Testalolone
17(β)-[1-ketoethyl]-Δ^{5}-*androstene*-3(β)-ol	Pregnenolone
17(β)-[1-ketoethyl]-*etiocholane*-3(β)-ol	Allo-pregnane-3(β)-ol-20-one
Δ^{16}-*androstene*-3(α)-ol	———
Δ^{16}-*androstene*-3(β)-ol	———

IV. Steroids isolated from the ovary

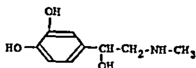
Systematic name in terminology of this book	*Other names*
$\Delta^{1,3,5,10}$-*estratriene*-3,17(α)-diol	α-estradiol
17(β)-[1-ketoethyl]-*androstane*-3(β)-ol	Allopregnanolone
17(β)-[1-ketoethyl]-Δ^{4}-*androstene*-3-one	Progesterone

V. Steroids isolated from the placenta

Systematic name in terminology of this book	*Other names*
$\Delta^{1,3,5,10}$-*estratriene*-3,17(α)-diol	α-estradiol
$\Delta^{1,3,5,10}$-*estratriene*-3-ol-17-one	Estrone
$\Delta^{1,3,5,10}$-*estratriene*-3,16(β),17(α)-triol	Estriol (also occurs as glucuronide)

Subsequently, *Stolz* (1905) and *Dakin* (1905) simultaneously, succeeded in preparing racemic *dl*-3, 4-dihydroxyphenylethanolmethylamine — that is to say, racemic adrenaline — at a time when their views concerning the chemical structure of the compound were not yet precise.

These observations are of considerable historic interest, since they represent for the first time, the isolation of a pure crystalline hormone and its synthesis They also show that the synthetic preparation of a hormone, can succeed even on the basis of very uncertain concepts concerning its structure. It was actually the synthesis of adrenaline and the subsequent work of *Friedmann* (1906), which definitely established that the hormone possesses the formula :



This was subsequently separated into the two optical isomers (*Flächer*, 1908).

Sympathin. — In 1902, *Langley* observed the similarity between the actions of adrenal extracts and those that follow sympathetic nerve stimulation. *Elliott* (1904) came to the conclusion that "adrenaline might then be the chemical stimulant liberated on each occasion, when the impulse arrives at the periphery," because of the great similarity between the effects of adrenaline administration and sympathetic nerve stimulation But it was not until 1921, when *Loewi* published the results of his now classical experiments, that the sympathin theory obtained experimental confirmation. *Loewi* showed that Ringer's solution, circulating through the isolated heart of a frog, can acquire sympathicomimetic properties following stimulation of the sympathetic fibers in the vagosympathetic nerve. (In the frog, vagal and sympathetic fibers course in a common nerve.) Such Ringer solution increases the pulse rate and the altitude of contractions, when applied to a second heart. *Loewi* termed the hypothetic substance, liberated during sympathetic stimulation, "accelerans substance" or, in German, "*Acceleransstoff*." In the same year *Cannon* and *Uridil* (1921) observed that stimulation of hepatic nerves liberates a substance into the blood stream, which increases the pulse rate of the denervated heart in the cat.

Subsequent investigators furnished ample evidence showing that sympathetic stimulation causes the liberation of a substance at the nerve endings in many organs innervated by "adrenergic," or adrenaline-imitating nerves. This substance has been termed "sympathin" (*Cannon* et al 1931). (Cf. p. 114.)

Hyperadrenalinism. — *Fränkel* was probably the first, in 1886, to describe a case of an adrenal tumor, which led to typical symptoms of hyperadrenalinism, that is, attacks of cardiac palpitation, anguish, dizziness, headache, hypertension and frequent epistaxis Death occurred suddenly in collapse Autopsy revealed tumors in both suprarenals. The neoplasms were thought to be angiosarcomas, but from the description given, it is evident that they were tumors of the chromaffin tissue.

The first cases, in which the causative neoplasm was correctly identified by the pathologists, were those of *Kolisko* (1910), *Herde* (1912) and *Helly* (1913).

In 1927, *C. H. Mayo* saw a woman, who suffered from repeated attacks of paroxysmal hypertension, pulmonary edema, pallor and vomiting. Exploratory operation revealed a tumor in the region of the left adrenal. Although the nature of this growth was not recognized at the time of the operation, it was removed and the patient

11

THE ADRENALS

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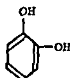
HISTORIC INTRODUCTION

The adrenals (or suprarenals) were apparently first described by *Eustachius* (1563) in his book "De Glandulis Quæ Renibus Incumbunt". It took more than 300 years, however, before any indication of their probable action was obtained. In those early days, when the public considered it sinful to dissect the human body, autopsies had to be performed in secret, often several days after death. By that time the medulla, which is highly subject to autolysis, was usually transformed into a viscous dark fluid ("atra bile"), within the more resistant cortex. Hence, the adrenals were thought to be capsules filled with liquid ("capsula suprarenalis").

Adrenaline. — *Vulpian* (1856) discovered that the cells of the adrenal medulla differ, in their staining ability, from those of the cortex. He noted that if a slice across an adrenal is immersed into a ferric chloride solution, the medulla takes a greenish tinge, while the cortex does not. Subsequently, *Henle* (1865) observed that certain granules in the medullary cells give a reddish-brown precipitate with dilute solutions of potassium bichromate, the so-called "chromaffin reaction." The use of this method enabled *Wiesel* (1904) to describe the chromaffin system as we know it today.

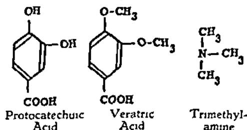
Pressor adrenal extracts were first prepared by *Oliver & Schäfer* (1894). The active principle of the adrenal medulla was subsequently isolated, in the form of its very insoluble benzoylate, as an amorphous but highly potent powder, by *Abel* (1899), who gave the name "epinephrine" to this ester. Still amorphous, but highly purified preparations of the hormone, were obtained by precipitation of the insoluble metallic salts of adrenaline and subsequent splitting of the latter (*v. Furth*, 1897-1903). Pure crystalline preparations of natural l-adrenaline were first described by *Aldrich* (1901) and *Takamine* (1901). The hormone itself was named suprarenin (*v. Furth*) or adrenaline (*Takamine*). The preparation of the hormone led to the determination of its empirical formula as $C_9H_{13}O_3N$.

The characteristic ferric chloride reaction (*Vulpian*, 1856), raised the suspicion that adrenaline is a pyrocatechol derivative.



Pyrocatechol

This was confirmed (*Takamine*, 1902) by showing that, on melting adrenaline with potassium hydroxide, protocatechuic acid is obtained, while, upon exhaustive methylation and subsequent oxidation, trimethylamine and veratric acid are formed (*Jowett*, 1904).



Protocatechuic Acid — Veratric Acid — Trimethylamine

which also occurs naturally in the adrenal cortex. This transformation helped to prove the close relationships existing between the testoids and corticoids and to elucidate the structure of the latter.

Since that time, a large number of steroids have been isolated from the adrenal cortex. While some of these are apparently inactive precursors or metabolites of hormones, others exhibit corticoid, testoid, luteoid, folliculoid and other pharmacologic activities. (See : The Steroids.)

The first in vitro production of a corticoid was accomplished by the partial synthesis of DESOXYCORTICOSTERONE (*Steiger* and *Reichstein*, 1937), from the plant sterol, stigmasterol, after first degrading the latter to 3-hydroxy-etiocholanic acid.

There still is considerable doubt concerning the true hormonal nature of desoxycorticosterone, although steroids with similar pharmacologic actions, are undoubtedly produced by the adrenal cortex.

It is of historic interest that the alleged isolation of this compound from the gland — and thus, the demonstration of its possible natural occurrence as a hormone — was, in any case, reported only after its synthesis (*Reichstein and von Euw*, 1938).

More recently, 11-DEHYDROCORTICOSTERONE (*Lardon and Reichstein*, 1943); CORTICOSTERONE (*v. Euw, Lardon and Reichstein*, 1944); 17-HYDROXY-11-DEHYDROCORTICOSTERONE (*Kendall's "compound E"*) (*Sarett*, 1945), have been prepared from desoxycholic acid. A good deal of work along these lines is now in progress in various laboratories, so that we have reason to believe that many additional naturally occurring cortical steroids will be available by synthesis and that the discouragingly small yields obtained will improve

Hypercorticoidism. — The first proven case of adrenal-cortical tumor was described by *Tilesius* (1803). In 1811, *W. Cooke* described the case of a 7-year-old girl with bilateral adrenal tumors, adiposity and marked hirsutism, especially around the external genital organs

During the subsequent century, several other cases were, more or less accurately, described but the subject received serious attention only after 1905, when *Bullock and Sequeira* published their famous report on 11 children, all under 15 years of age.

Bovin was probably the first, in 1909, to "cure" a female pseudohermaphrodite by removing an adrenal tumor.

It was not until quite recently, however, that chemists have shown us the existence of a variety of steroids in the adrenal cortex and pharmacologic assays revealed that many of these possess qualitatively distinct activities This has raised the possibility that the various manifestations of the adrenogenital syndrome (pseudohermaphroditism, hypertension, diabetes, adiposity, etc.), are not necessarily due to the excess production of one adrenal-cortical hormone. The relative preponderance of one or the other symptom, in individual cases, thus becomes understandable.

The production of nephrosclerosis and hypertension, in the absence of any sexual anomaly, in experimental animals treated with desoxycorticosterone, led us to suppose that a selective increase in the endogenous mineralo-corticoid production of the cortex, may be the cause of corresponding syndromes in man. The concept of the "diseases of adaptation" was largely based upon this observation, since it is known that certain corticoids are produced in excess, during adaptation and defence to any type of damaging agent.

became symptom-free. In the first publication, the pathologic diagnosis was "malignant blastoma," but subsequent studies, by the same author, showed it to be a pheochromocytoma.

Addison's Disease. — Descriptions of clinical cases, exhibiting the syndrome of adrenal-cortical insufficiency, have been described in the earliest medical literature. It was not until 1855, however, that the English physician, *Thomas Addison*, called attention to the accompanying adrenal lesions, which he considered of pathogenic significance. *Addison's* admirably concise description of the disease, *which now bears his name, deserves to* be quoted :

"The leading and characteristic *features of the morbid state, to which* I would direct attention are, anemia, a general languor and debility, a remarkable feebleness of the heart's action, irritability of the stomach and a peculiar change of colour of the skin occurring in connection with a diseased condition of the suprarenal capsule."

His publication was of the greatest importance for the development of endocrinology as a whole, since it gave the first tangible proof of the important rôle played by the endocrines in internal medicine. Even before *Addison*, some morphologists theorized on the possible functional significance of the endocrine glands in general and the adrenals in particular, but his now classical monograph, gave one of the strongest motives for the work of the pioneers, who directed their attention to this field. *Sir William Osler* (1896) was the first to use (successfully?) an adrenal extract in the treatment of Addison's disease, but it was not until about 20 years ago that consistently active cortical preparations became available

Corticoids. — The first adrenalectomies were performed by *Brown - Sequard* (1856), who concluded that these glands are essential for the maintenance of life. However, it appears very probable that the death of his animals was due to inappropriate surgical technic, since even unilateral adrenalectomy was fatal in his hands. As in his famous report on the activity of the testis extracts, the "father of endocrinology" succeeded in drawing a correct conclusion from faulty experiments.

That *adrenaline is not the only hormone* of the adrenals, and that the substance necessary for the maintenance *of life actually originates in the cortex*, has been demonstrated on elasmobranch fish, such as the torpedo, in *which the cortex forms a separate* organ. Here the cortex can be removed without injury to the medulla and this *is followed by the appearance of typical* deficiency symptoms and death (*Biedl*, 1910). It was later shown, in the United States, that adrenalectomized dogs and cats can be kept alive almost indefinitely, by the continued administration of adrenal-cortical extracts (*Rogoff* and *Stewart*, 1925; *Hartman* et al. 1928; *Swingle* and *Pfiffner*, 1931). Subsequent work led to the *isolation from the cortex* (mainly of cattle) of several crystalline compounds with high corticoid activity (*Grollman and Firor*, 1933, *Kendall* et al. 1935; *Wintersteiner and Pfiffner*, 1935). Several of the early crystalline fractions were probably mixtures, but they were sufficiently pure to be identified as steroids and hence as close relatives of the ovarian and testicular hormones.

In 1936 *Mason, Kendall et al.* in the U.S.A., isolated their compounds "A" and "B," which are identical with DEHYDROCORTICOSTERONE and CORTICOSTERONE respectively. Almost simultaneously, in Switzerland, *Reichstein* (1936) succeeded in isolating corticosterone from the adrenal cortex *and the* same author showed that several cortical steroids can be transformed into "ADRENOSTERONE," *a testoid compound.*

making the border line between them rather indistinct. The medullary cell is polygonal: it measures about 18-30μ and its vesicular nucleus about 6-8μ in diameter. One of the most characteristic features of the medullary cells is their chromaffinity, which is a good index of their adrenaline content. The bichromate reaction is based upon the fact that the intracellular adrenaline granules give a typical color reaction, with dilute solutions of potassium bichromate. The reddish-brown tinge of the reaction product is a combination of the brown color of the reduced



F· . · c of the normal adrenal (t ··, ,· — Under the connective tissue capsule are the acinus-like dark cell-groups of the glomerulosa (G), these are followed by the almost straight, light (richest in lipids) cell-columns of the fasciculata (F) and then by the interlacing strands of the reticularis (R) Only a small part of the medulla (M) is visible underneath the cortex



I ance of the normal adrenal (I ..man)i — Note distinct glomerulosa (G) and fasciculata (F) while reticularis (R) is less prominent. Medulla (M) shows signs of beginning autolysis

chromate and the red of the adrenaline oxidation products Since, in the test tube adrenaline gives a similar "chromaffin reaction" with potassium bichromate solutions, it is generally agreed that the hormone itself, or precursors closely related to it, are responsible for this histo-chemical reaction

The ADRENAL CORTEX consists of three structurally different layers The external zone, immediately under the connective tissue capsule, is called the *zona glomerulosa.* Its cells are small, poor in cytoplasm and more or less irregularly arranged The nuclei are small and rich in chromatin. Inside this layer is the *zona fasciculata,* which consists of regular rows of large polygonal cells with vesicular nuclei. The cell

NORMAL MORPHOLOGY

ANATOMY

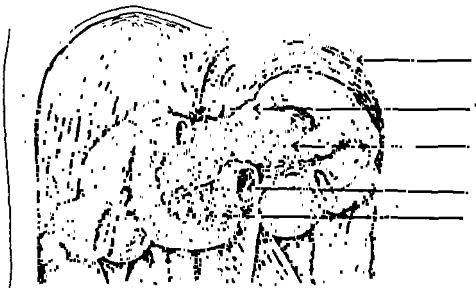
In man the adrenals are paired organs situated in the retroperitoneal space, close to the upper pole of each kidney and separated from the latter by a layer of fat tissue. The right adrenal has the shape of a *pyramid* and is *situated* directly above the upper pole of the kidney, while the left adrenal is crescent-shaped and lies more on the anterior and medial kidney surface. Both kidney and adrenal are surrounded by the same firm renal fascia and a common adipose capsule. The suprarenals are located at the height of the 11th or 12th thoracic to 1st lumbar vertabræ: the right adrenal is adherent to the liver and the inferior vena cavæ, the left is completely covered with peritoneum on its anterior surface and does not adhere to any organ.

The surface of the adrenal is irregular, with many furrows. On the cut surface, the naked eye readily distinguishes the yellow outer CORTEX from the reddish-brown inner cortex and the grey MEDULLA. The latter is highly subject to post-mortal autolysis Although there is no clear-cut evidence of any direct functional interrelation between cortex and medulla, the former surrounds the latter in a capsule-like manner in all mammals. In some of the lower vertebrates, the two types of cells tend to be even more closely intermingled. (See : Comparative Morphology.)

The SIZE of the adrenal is subject to great individual variation, but averages about 45 × 25 × 6 mm. in width, height and thickness, respectively; its total volume is about 5 cc. The weight of the two adrenals averages about 10 gm. in the normal individual. The higher "normal" weights, given in some textbooks, are derived from observations on patients who died from diseases, almost all of which cause adrenal enlargement, owing to the general-adaptation-syndrome elicited by them.

HISTOLOGY

The histologic structure of the ADRENAL MEDULLA is quite different from that of the cortex. Hence differentiation between the two is not difficult, although cell cords of the cortex may reach deep into the medulla and vice versa, thus



Position of adrenals and pancreas in relation to other abdominal organs.
(Redrawn after H Gray, "Anatomy of the Human Body", Lea & Febiger, 1942)

portant nerve tracts course to the adrenals from the semilunar ganglion and the renal plexus. All adrenal nerves reach the medulla and form intimate connections with its cells after merely traversing the cortex. The cortical cells themselves receive no important nerve endings (See also p 115.)

The vagus is not known to participate in the innervation of the adrenals.

A large number of GANGLION CELLS are seen on the surface and in the medulla of the human adrenal, especially in the hilum region. Most of these are multipolar, a few bi- or unipolar. They probably represent peripheral nerve centers.

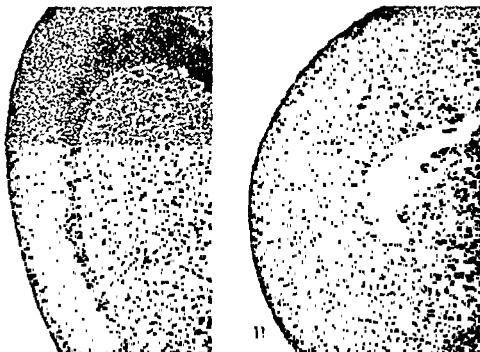
COMPARATIVE MORPHOLOGY

The presence of the adrenaline-containing, chromaffin cells has been demonstrated in INVERTEBRATES (most annelides, mollusca, cephalopodes) and in cyclostomata, where they are usually found in close connection with large vessels and nerve tracts. Cortical cells, on the other hand, do not appear in animals lower than the vertebrates.

In SELACHIANS, unlike in most other animals, the adrenal cortex (or "interrenal body," as it is called in these fish) is anatomically distinct from the chromaffin accumulations. This is of special interest because it permits the separate removal of cortical tissue without injury to medullary cells.

In AMPHIBIA there is no distinct demarcation between cortical and medullary cells, the two being intimately intermixed. In some amphibia, adrenaline-like substances are produced in the mucous glands of the skin, but it remains to be seen whether there is any relationship between these glands and the adrenal system. In REPTILES and BIRDS the cortical and medullary cells are also irregularly intermingled, there being no separate cortex and medulla.

Among the MAMMALS, the adrenal medulla is always surrounded by a dis-



Adrenal with "X-zone". — A. Dark, cellular X-zone in reticularis region of the adrenal in a castrate male mouse. — B. Adrenal of a similar castrate male mouse 25 days after subcutaneous implantation of a 12 mg pellet of methyl-testosterone Note complete disappearance of "X-zone".

columns are radially arranged, and run parallel with each other, from the outer zone towards the medulla. Between them are radially coursing sinusoids, whose walls are studded with littoral, reticulo-endothelial cells. *The zona reticularis* is the innermost layer of the cortex, immediately adjacent to the medulla. It consists of very irregular strands, which form a network of small cells with dark nuclei. Many melanin *and iron-pigment containing* phagocytes are found in this zone. The development of the glomerulosa and reticularis are subject to great individual variations, but the fasciculata is always the widest zone

Because of the numerous lipid granules, the cortical cells, especially in the fasciculata, have a vacuolized cytoplasm *and are designated as "spongiocytes."* Around the central vein, the cortex may be invaginated into the medulla, thus forming the "central cortex" or "inverted cortex"

The REGENERATION and growth of the adrenal cortex has been claimed to occur mainly from *the glomerulosa*, whose cells gradually migrate through the fasciculata into the reticularis and eventually succumb in this latter zone. However, this view is not unanimously [illegible] in [illegible] do [illegible] dis-posed zone.

Islets of LYMPHATIC TISSUE and round cell infiltration are rather common in human adrenals, especially under certain pathologic conditions. (See Addison's Disease.)

Three *adrenal* ARTERIES, derived respectively from the aorta, inferior phrenic and renal arteries, supply each of the two adrenals. They form a rich subcapsular plexus, from which the blood flows through the cortical *sinusoids into* the medulla; here it gathers in a large *central* VEIN, leaving the organ at the hilum. The right adrenal vein *discharges its blood directly into the* inferior vena cava, while the left empties into the renal vein. *Hence, tumors of* the left adrenal tend to invade this vein. The adrenal arteries enter the gland at various points of the surface, the vein emerges at the hilum. The adrenals *are extraordinarily well supplied* with blood, receiving about 6 to 7 cc. per gm. of tissue, per minute. All of this blood flows through the cortex before reaching the medulla, so that the latter is exclusively supplied by venous *blood, maximally saturated with the* metabolites of the cortical cells. The physiologic significance of this arrangement is not known. In addition to the large central veins, small venules leave the gland at various points of the capsular surface; some of these form anastomoses *with the renal veins.* This may be of physiologic importance, since through these veins blood, saturated with adrenal hormones, may directly enter the kidney. There are important muscular sphincters in the wall of the central vein. Their periodic contraction and *relaxation helps to collect* and release large amounts of hormone saturated blood, in accordance with the requirements of the organism.

The LYMPHATICS emerge from the gland, around the central vein, in the hilum.

The adrenal NERVES *are derived from* the great splanchnic, after having passed through the suprarenal plexus They are preganglionic, medullated fibers which are not interrupted by cell stations along their course. Transection of the splanchnics, above the semilunar ganglion, causes degeneration of the adrenal nerves, which proves that these pass through the ganglion without interruption. Thus they appear to differ from other sympathetic pathways Ac*tually the nerve cells, and the* embryologically related chromaffin cells of the medulla, correspond to the ganglion and the postganglionic fibers. Less im-

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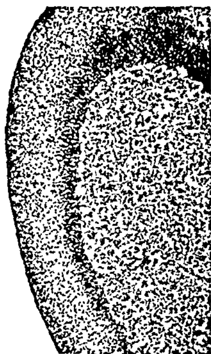
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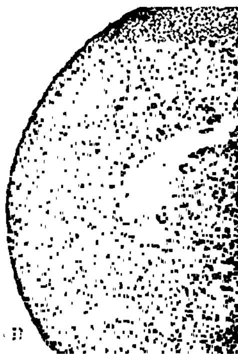
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A



B

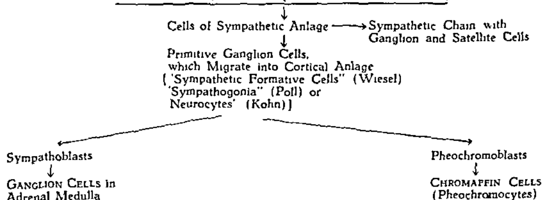
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tinct cortex, but the size and shape of the gland is extremely variable. In the small laboratory rodents, the adrenals are roundish or oval and their surface is smooth, while in most of the larger mammals the cortical surface is corrugated, as it is in man. The *guinea pig* adrenal is noteworthy because of its extraordinarily large size. In certain strains of *mice* the reticularis is especially prominent and often designated as the "X-Zone." There is reason to believe that the cells of this zone are the source of adrenal testoids. It is interesting that the cortex is much larger in the wild, than in the laboratory *rat*. (Exposure to strain? Diet?)

EMBRYOLOGY

The adrenal CORTEX is formed from a thickening of the celomic epithelium, in the region between the two renal (pronephros) primordia. It begins to be clearly distinguishable in embryos of 5.6-8.5 mm. crown-rump length Lipid granules are first observed in 2.5-5 cm. embryos. The fetal adrenals (in common with similar tissues, such as the corpus luteum) have a particular affinity for ponceau fuchsin. The postnatal persistence of fuchsinophilic granules in the reticularis is frequently associated with *pseudohermaphroditic traits*, as we shall see later. (See p. 163.)

The MEDULLA develops from the primordium of the sympathetic nervous system, which in turn arises from the neuroectoderm. The primitive sympathetic anlage is the common precursor of the sympathetic chains, the ganglion cells in the medulla and the chromaffin cells themselves. The terms "sympathogonia" (Poll), "sympathetic formative cells" (Wiesel) and "neurocytes" (Kohn) have all been used to designate intermediate cell types in the course of the development of the adrenal medulla. This development may be schematically illustrated as follows ·



Any of the above cell types may give rise to tumor formation.

In man the invasion of the adrenal cortex, by the primitive ganglionic cells, occurs in embryos of 15-17 mm crown-rump length. The invading cells continue to proliferate and to differentiate in their new location, even during early postnatal life

The PARAGANGLIA are slightly chromaffin cell accumulations found, in contact with sympathetic ganglia, outside the adrenal medulla They develop from the same type of primitive ganglionic cells which form the adrenal medulla. These extra-adrenal chromaffin cells represent an additional source of adrenaline, yet their ability to

compensate for the loss of adrenal chromaffin cells is very limited, as judged by the behaviour of adrenalectomized animals.

The SIZE of the adrenals, in proportion to the other organs of the body, reaches a certain maximum in 4-week-old human embryos. In these the adrenal is as large, or larger, than the kidney. In the new-born the adrenal is one-third, and in the adult 1/28, as large as the kidney. A particularly pronounced and rapid involution, especially of the cortical portion, occurs during the first few days of postnatal life; perhaps because of the sudden withdrawal of maternal hormonal influences. (See p 135)

THEORIES CONCERNING THE HISTOPHYSIOLOGY OF THE ADRENALS

It is generally conceded that the CHROMAFFIN GRANULES in the medullary cells are actually adrenaline itself or its precursor. In any case, the amount of chromaffin material histologically demonstrable in the medullary cells, closely corresponds to the amount of adrenaline, as determined by analytic or bioassay methods. Histologic observations show that the adrenaline granules are discharged directly into the medullary sinusoids.

The LIPID GRANULES in the cortical cells are not the hormones of the cortex, but consist mainly of cholesterol and neutral fats. Since, however, the cortical hormones are highly fat-soluble (much more soluble in fats than in plasma) it is probable, that the visible lipid granules act as solvents in which the cortical hormones are stored.

It remains unexplained why, in all vertebrates (except certain fish), the primordia of the medulla travel a long distance in order to unite with those of the cortex. All the blood reaching the medulla, has to travel through the cortical sinusoids first; this suggests that products of the cortical cells may have to undergo further transformation in the medulla, but such a possibility is entirely conjectural. Since both cortical and medullary hormones play an important rôle in the general-adaptation-syndrome, the demand for both types is especially great during exposure to non-specific damage. (See : General-Adaptation-Syndrome.) Perhaps the ANATOMIC UNION OF THE TWO GLANDS is advantageous because, during emergencies, relaxation of the sphincters in the adrenal veins suddenly supplies the general circulation with large amounts of both cortical and medullary hormones, stored in the gland's spacious sinuses.

The tendency of the adrenals to acquire a flattened corrugated shape, in the course of evolution, results in the development of a very large contact-surface between cortex and medulla. This may also be cited as suggesting the existence of close functional correlations between the two parts of the glands.

Stimulation of the adrenal NERVES elicits an immediate release of chromaffin granules into the blood stream, without causing any detectable secretion of cortical lipid granules. Conversely, denervation of the adrenals prevents the secretion of adrenaline, without interfering with cortical function. Hence, it may be concluded that the secretion of cortical hormones is not significantly influenced by specific secretory nerves, while that of adrenaline is almost entirely dependent upon nervous stimuli

The high concentration of ASCORBIC ACID in the adrenals suggests that this vitamin may play an important rôle in the biogenesis of cortical hormones and adrenaline, but this has not been proven.

CHEMISTRY OF THE ADRENALS

CHEMICAL COMPOSITION OF THE GLAND

The chemistry and biogenesis of the adrenal hormones will be discussed in subsequent chapters Here we shall merely consider the most important data concerning the general chemical composition of the gland.

The adrenals — like most other tissues — contain approximately 80% WATER.

The CARBOHYDRATE content of the adrenals is extremely low, although there are traces of glycogen and rather large amounts of LACTIC ACID (about 0 2% of the wet weight) in it.

The cortex is particularly rich in LIPIDS. Most of these form distinct cytoplasmic granules. Considerable quantities of fatty acids, cholesterol, cholesterol esters, phosphatides and lipochromes (e.g., carotene and xanthophyll), have been isolated from the adrenal cortex These lipids and lipochromes are responsible for the light, yellowish color of the cortex.

About two-thirds of the dry material of adrenal tissue is PROTEIN, but so far its specific characteristics have not been adequately studied

Among the INORGANIC CONSTITUENTS, a comparatively high concentration of iodine, bromine, iron and sulphur are noteworthy. The latter two probably are of importance in the formation of the pigment granules in the zona reticularis

Various ENZYMES have been demonstrated in the adrenals Lipases appear to play an important rôle in the discharge of lipid granules. A high concentration of proteases has been held responsible for the unusually rapid, postmortal autolysis characteristic of these glands, while oxidases, decarboxylases, etc., appear to play an important part in the biogenesis of adrenaline and its subsequent transformation into inactive oxidation products. (See: Biogenesis of Adrenaline.)

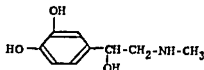
The high VITAMIN C content has already been mentioned in connection with histologically demonstrable cell inclusions.

The fact that the adrenals are rich in "PLASMALOGENS", CHOLINE and GLUTATHIONE has provoked much speculation concerning the possible rôle of these compounds in adrenal physiology, but this question still awaits clarification

CHEMISTRY OF THE ADRENAL HORMONES

Chemistry of Adrenaline. — The only hormone known to be produced by the adrenal medulla is adrenaline.

It exists in two optically isomeric forms, but only l-adrenaline occurs in nature Its structure is :



Adrenaline is very sensitive to the action of oxidizing agents. (See Fate of Adrenaline in Body) It is usually administered in the form of the highly water-soluble hydrochloride

Chemistry of Adrenaline Derivatives (with their chief biologic characteristics). — It is not within the scope of this book to discuss the chemistry of the, very numerous and pharmacologically important, derivatives of adrenaline It should be emphasized, however, that some derivatives of the hormone are valuable sympathomimetic drugs, that is, they stimulate structures innervated by adrenergic nerves Many of these compounds possess definite advantages over adrenaline Some exhibit one or the other desired action in a more specific manner than the hormone itself (that is, with less of the undesired side effects), while others have a compara-

tively greater oral activity, a more prolonged action or a lesser toxicity. Many of the, pharmacologically important, adrenaline derivatives occur naturally in plants (ephedrine), as animal poisons (toad venoms) or at sympathetic nerve endings (sympathin), while others are artificial compounds obtainable only by synthesis. — Little is known about the mechanism of their action. Some (e.g., ephedrine) are claimed to act merely because they are destroyed by the same amineoxydase which inactivates adrenaline. Thus they protect the hormone from rapid destruction, since they successfully compete with it for this enzyme.

The most important adrenaline derivatives, with some of their outstanding characteristics, are listed below:

Name of Compound	Formula	Characteristics
ADRENALINE 1-hydroxy-1-(3,4-dihydroxyphenyl)-2-methylaminoethane *Syn*: Adrenalin, Epinephrin, Suprarenine	OH, OH $HO\text{-}CH\text{-}CH_2\text{-}NH\text{-}CH_3$	Naturally occurring hormone of the adrenal medulla. Its characteristics are described in the text, the compound being mentioned here merely for purposes of comparison with its derivatives. Presumably identical with sympathin I, which has also been termed 'Sympathin A'. (Cf. p. 114.)
ADRENALONE 1-keto-1-(3,4-dihydroxyphenyl)-2 methylaminoethane *Syn*: Kephrine, Styphon	OH, OH $O{=}C\text{-}CH_2\text{-}NH\text{-}CH_3$	The ketone corresponding to adrenaline. It has marked sympathomimetic effects, although its pressor action is comparatively mild. Used mainly for its local action as a hemostatic, because of its prolonged action and low systemic toxicity.
ADRENOXINE	?	An oxidation product of adrenaline obtained by treatment with tyrosinase. It exerts acetylcholine-like negative chrono- and inotropic effects and decreases the blood pressure. It has been advocated as an antihypertensive drug. (Cf. p. 109.)
ARTERENOL 1-hydroxy-1-(3',4-dihydroxyphenyl)-2-aminoethane *Syn*: Nor-adrenaline	OH, OH $HO\text{-}CH\text{-}CH_2\text{-}NH_2$	A demethylated adrenaline. It was claimed to be identical with "Sympathin E", because it elicits mainly excitatory effects which cannot be inhibited by ergotamine. Its pressor action is even greater than that of the natural hormone. It has also been designated as 'Sympathin N'. (Cf. p. 114.)
BENZEDRINE 1-phenyl-2-aminopropane *Syn*: Mecodrin, Simpanin, Amphetamine	CH_3 $CH_2\text{-}CH\text{-}NH_2$	Pharmacologically similar to ephedrine, differing from the latter mainly by its greater ability to stimulate mental processes. Used as a vasoconstrictor for inhalation and local application in rhinology, to stimulate nervous centers in narcolepsy, postencephalitic parkinsonism and mental fatigue (instead of caffeine), also in various allergic conditions. (May lead to addiction.)
COBEFRIN 1-hydroxy-1-(3',4-dihydroxyphenyl)-2-aminopropane *Syn*: Cobrastil	OH, OH CH_3 $HO\text{-}CH\text{-}CH\text{-}NH_2$	Has no material advantages of adrenaline but is sometimes used as a substitute for the latter, especially in combination with cocaine derivatives for infiltration anesthesia.

Name of Compound	Formula	Characteristics
EPHEDRINE 1-hydroxy-1-phenyl-2-methylamino-propane	CH_3 HO-CH-CH-NH-CH_3	Pharmacologically similar to adrenaline but 1,000 times less active Has advantage over hormone that it is orally active and exerts more prolonged effect Unlike for the hormone, organs are not sensitized to it either by cocaine or by denervation perhaps because it attacks the muscle directly It is used as an analeptic, mydriatic with minimal effect on ocular tension, respiratory stimulant and in allergic conditions such as hay fever and asthma *Pseudo-ephedrine* differs from ephedrine only in the steric position of the alcoholic hydroxyl It has no notable pharmacologic advantages
PAREDRINE 1-(4 -hydroxyphenyl)-2-amino-propane *Syn* Neo-ephedrine	OH CH_3 CH_2-CH-NH_2	Differs from tyramine only in having an additional methyl group Pharmacologically resembles adrenaline, but is practically devoid of actions on central nervous system Used mainly as a mydriatic and for production of temporary cycloplegia
PAREDRINOL 1-(4'-hydroxyphenyl)-2-methyl-aminopropane *Syn* Veritol	OH CH_3 CH_2 CH-NH-CH_3	Differs from paredrine only in possessing an additional methyl group on amino nitrogen. Orally active pressor agent used in various circulatory disturbances
PROPADRINE 1-hydroxy-1-phenyl-2-aminopropane *Syn* Nor-ephedrine Mydriatine	CH_3 HO-CH-CH-NH_2	Differs from ephedrine only in that it lacks methyl group on amino nitrogen. Pharmacologically similar to ephedrine
SYMPATOL 1-hydroxy-1-(4'-hydroxyphenyl)-2-methylaminoethane	OH HO-CH-CH_2-NH-CH_3	Differs from adrenaline only in the absence of the meta-phenolic hydroxyl group 50 to 100 times less active than the hormone Its pressor effect is more prolonged than that of adrenaline and unlike the latter, it is claimed not to increase the pressure in the auricles of the heart and is less likely to produce fibrillation SYNEPHRINE is racemic sympatol which essentially shares the actions of the latter NEO-SYNEPHRINE differs from synephrine only in that the phenolic hydroxyl is on C_3 It is used for local application to mucous membranes, in allergic conditions for sustaining the blood pressure during spinal anesthesia It can be given parenterally or orally and is less likely to cause cardiac arrhythmias than adrenaline
TYRAMINE 1-(4 -hydroxyphenyl)-2-amino-ethane	OH CH_2-CH_2-NH_2	Formed by action of bacteria upon protein as a result of tyrosine decarboxylation Shares some of the effects of adrenaline (e g pressor action stimulation of uterine muscle), but has no clinical applications as a sympathomimetic compound

Chemistry of Cortical Hormones. — All the cortical hormones, known up-to-date, are steroids. Their fundamental chemical characteristics have been described in the section on the steroids.

GENERAL PHARMACOLOGY OF THE ADRENAL HORMONES

STANDARDIZATION

Analytic Methods for the Detection of Adrenaline. — *The direct gravimetric determination of adrenaline can rarely be employed because of the minute quantities present in body fluids and tissues.* Hence, usually, colorimetric methods are used. Some of these are based on the property of adrenaline to form colored products when oxidized with various agents; others depend upon the formation of a colored reduction product from reagents exposed to the hormone; yet others on special reactions, due to the pyrocatechol ring in the adrenaline molecule. The most commonly used adrenaline reactions are the following :

(1) The FERRIC CHLORIDE REACTION (*Vulpian*, 1856). Neutral, or slightly acid, solutions of adrenaline give an intense, emerald-green reaction with ferric chloride, due to the phenolic hydroxyl of the adrenaline molecule. Pyrocatechol derivatives give the same reaction and hence interfere with its specificity. (Sensitivity about 1:10,000,000 under optimal conditions.)

(2) The IODINE REACTION (*Vulpian*, 1856). Free iodine causes a pink discoloration of adrenaline solutions due to partial oxidation of the hormone. (Sensitivity 1:2,000,000.) It is best to perform the iodine reaction in acid solutions and to read the coloration with Pulfrich's photometer. Adrenaline may then be detected by its green absorption band at 500$\mu\mu$ (*v. Euler*, 1933)

(3) The IODATE REACTION (*Krauss*, 1909) is also based on the oxidation of adrenaline by free iodine, but here the halogen is freed from the iodate by the hormone. The sensitivity of the reaction may be increased, by the addition of sulphanilic acid, so that dilutions of 1:5,000,000 are still detectable.

(4) The SUBLIMATE REACTION (*Comessatti*, 1909) is based on the oxidation of adrenaline by sublimate. (Sensitivity about 1:1,000,000.)

(5) The SUBLIMATE-IODATE-SULPHANILIC ACID REACTION (*Ruffmann*, 1922; *Bacq*, 1932; *Viale*, 1933) depends upon the successive sensitization of the iodate reaction by sulphanilic acid and of this reaction by sublimate (chain sensitization). (Sensitivity 1:400,000,000, under optimal conditions.)

(6) The PERSULPHATE REACTION (*Ewings*, 1910) has the advantage that it can be performed even in colored organ extracts since the persulphate decolorizes them. (Sensitivity about 1: 500,000,000.)

(7) OTHER REACTIONS, BASED ON THE OXIDATION OF ADRENALINE, use gold chloride, manganese superoxide, potassium ferricyanide, bromine, chlorine, calcium chlorate, ammoniacal silver reagent, potassium bichromate, ammonium molybdate, sodium tungstate or diazobenzenesulphonic acid, etc., *all of which* yield colored products on contact with adrenaline Unfortunately, none of these color reactions have proven to be very specific or accurate, especially in the presence of contaminating substances.

(8) The SPECTROGRAPHIC DETERMINATION of adrenaline (*Handovsky and Reuss*, 1928) is based on the fact that the hormone shows an absorption band in the ultraviolet, with a maximum at 280$\mu\mu$. The method gives encouraging results It has also been used for the determination of sympathin, which exhibits an identical absorption spectrum

(9) The green FLUORESCENCE of adrenaline solutions during ultraviolet irradiation, in the presence of alkali and oxygen (*Gaddum and Schild*, 1933; *Loewi*, 1936), has a sensitivity of 1:10^{9}. This method can also be used for sympathin and gives results which check well with bioassays.

Among the analytic methods, the spectrographic technics tend to give the

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TYRAMINE 1-(4'-hydroxyphenyl)-2-aminoethane	OH CH_2-CH_2-NH_2	Formed by action of bacteria upon protein as a result of tyrosine decarboxylation. Shares some of the effects of adrenaline (e g, pressor action stimulation of uterine muscle) but has no clinical applications as a sympathomimetic compound

Chemistry of Cortical Hormones. — All the cortical hormones, known up-to-date, are steroids. Their fundamental chemical characteristics have been described in the section on the steroids.

test object (such as the intestinal segment).

It will be noted that the denervated iris and the denervated heart are suitable for "internal bioassay technics," that is, the measurement of endogenous adrenaline.

(7) THE BLOOD PRESSURE OF THE CAT (*Elliot*, 1905; *Rosenblueth*, 1932) is perhaps the most suitable indicator for routine use, since the rise in blood pressure is almost strictly proportional to the dose of adrenaline injected. Usually male cats weighing 3 to 4 Kg are anesthetized with chloroform or ether, than tracheotomized and artificially ventilated. Following this the brain is removed, the spinal cord destroyed to the level of the 4th thoracic segment, and both vagi are cut. This operation causes a sudden decrease in the blood pressure to a level of 40-50 mm. of Hg, but it then remains quite constant, at this level. By comparing the effect of unknown and standardized solutions one can determine the adrenaline concentration, changing the dose of the unknown until the rise in blood pressure equals that caused by the standard of known concentration. With an arithmetic increase of the amount of adrenaline administered, the pressor effect increases logarithmically. This may be expressed by the formula $Kx = \frac{y}{A-y}$. In this formula x = concentration and y = action as % of the maximal action A. 0.07γ per Kg. suffices to produce a just perceptible rise in blood pressure, while 90γ per Kg causes a maximal increase.

Many other actions of adrenaline may be used as indicators in bioassays. Furthermore, even the tests described here may be varied, by using animal species other than those recommended above. For instance, the vasoconstrictor action may also be tested on the perfused hind-leg preparation of the frog (*Lawen*, 1904; *Trendelenburg*, 1910), the improving effect of adrenaline upon the heart action may be studied on the perfused frog heart, rendered hypodynamic by aconitine, etc. A detailed description of all these bioassays would exceed the scope of this book, especially since most of them are too laborious to be useful in the clinical diagnosis of hyperadrenalinism.

Bioassay of Corticoids. — Bioassay of the cortical hormones gives far more satisfactory results than the chemical methods. Folliculoid, luteoid and testoid compounds of the adrenal cortex are assayed in the same manner as the corresponding gonadal hormones. (See: Ovary and Testis.) The corticoids themselves do not represent a pharmacologically uniform group and different bioassay technics have been worked out to estimate the different types of corticoid activity.

A. LIFE MAINTAINING ACTIVITY:

(1) IN THE DOG (*Swingle and Pfiffner*, 1932). This test is based upon the ability of corticoids to maintain adrenalectomized animals in good condition. The "dog unit" is defined as the minimum daily dose per Kg. of body weight, which, when given over a period of 7 days, maintains health and a normal blood urea level.

(2) IN THE RAT (*Kutz*, 1931; *Grollman and Firor*, 1933). This test is based upon the ability of corticoids to maintain immature, adrenalectomized animals alive and to permit their growth. Usually immature males of 40 to 50 gm. are adrenalectomized and given two daily subcutaneous injections of the unknown preparation, in oil solution. The unit is defined as the minimum amount necessary to maintain the health and growth, of such rats, during a period of at least 14 days. There are several variants of this test since some workers prefer slightly larger or smaller animals, while others recommend the use of castrates, because of the occa-

more satisfactory results, but for most purposes bioassay methods are preferable, because they are more specific and in general also more sensitive. The substances likely to interfere with the colorimetric determination of adrenaline are, the less active optical isomer of the hormone, ascorbic acid and some other reducing substances.

Analytic Methods for the Detection of Corticoids. — While there are no satisfactory methods for the chemical determination of corticoids, rather encouraging results have been obtained with technics based upon the glucose-like reducing properties of their glycol side-chain (*Talbot*, 1945; *Sobel*, 1945).

Lowenstein et al. (1946), described a method for the determination of corticoids in the urine, based upon periodate oxidation of the primary alcohol group at C_{17}[2]. This yields one mol of formaldehyde per mol of oxidized corticoid and the formaldehyde is determined. (The method is not yet practical.)

Bioassay of Adrenaline. — Among the many bioassay technics used for the estimation of adrenaline in its solutions, the following deserve special attention ·

(1) Intestinal Segment of Rabbit (*Langley*, 1901; *Cannon and La Paz*, 1911). The peristaltic movements of a loop of rabbit intestine (suspended in oxygenated Ringer solution) are inhibited by adrenaline By comparing the potency of unknown solutions, with those containing adrenaline in known concentrations, the hormone content of various fluids can be estimated with a fair degree of accuracy.

(2) Segment of Non-Pregnant Rabbit Uterus (*Frankel and Allers*, 1909). Adrenaline stimulates the contractions of such a preparation in vitro

(3) Isolated Arterial Rings (*Friedmann*, 1904; *Rothlin*, 1920). A ring of a small artery (from cattle, pig or sheep) is suspended in Locke's solution and attached to a lever, which registers its contractions on a kymograph. Adrenaline causes contractions of the arterial rings, when added to the *suspension fluid.*

(4) The Denervated Eye. Removal of the sympathetic superior cervical ganglion greatly increases the adrenaline sensitivity of the pupil in the rabbit (*dilatation*) and of the nictitating membrane in the cat (contraction) (*Meltzer and Auer*, 1904; *Rosenblueth and Cannon*, 1932). The adrenaline concentration of fluids is tested by instilling them into the conjunctival sack of an animal whose pupil is thus denervated. The test may also be performed on the enucleated eye of the frog, which reacts to the hormone with mydriasis (*Lewandowsky*, 1898).

(5) The Denervated Heart (*Cannon*, 1922). Following transection of the vagi, combined with removal of the stellate and second thoracic ganglia of the sympathetic chain, the heart is completely deprived of nervous control. Conditions which cause adrenaline liberation from the animal's own adrenal medulla, increase the pulse rate of the denervated heart. Detectable tachycardia is produced by as little as one part of adrenaline in fourteen hundred million parts of blood.

(6) The Caval Pocket (*Stewart and Rogoff*, 1916). The inferior vena cava, of the dog or cat, is clamped below the entrance of the adrenal veins and just below the diaphragm. All veins entering this caval pocket are ligated, except those of the adrenals. The iris of the experimental animal is denervated as in test 4. After a certain period the upper clamp is removed. Dilatation of the pupil occurs if adrenaline has *been secreted during the interval whilst* the upper clamp was closed. If quantitative determinations are required, the blood collected in the caval pocket may be aspirated through a cannula and directly tested, in vitro, upon another

various modifications of this test, adrenalectomized mice or rats are given corticoid compounds, during a period of fasting; the amount of liver glycogen deposited, or the maintenance of the initial glycogen levels act as indicators of gluco-corticoid activity. A high carbohydrate, low potassium diet and 0.9% NaCl as drinking fluid are given to the animals, during 4 days after adrenalectomy, prior to the test. The results are expressed in comparison with the potency of known extracts in order to obtain comparable results. Some of the modifications of this technic are so sensitive that they detect active gluco-corticoids in doses of about 10 γ per animal.

(4) ANTI-INSULIN TEST (*Jensen and Grattan*, 1940). Male mice (18-22 gm.) are divided into groups of 20 animals each. At the onset of a six hour fast they receive subcutaneous injections of the unknown preparation in 0.2-0.5 cc. of oil. At the end of the fasting period, each animal receives 1.5 or 2 units of insulin per Kg. of body weight and is maintained at a temperature of 34° C. *The percentage of* animals protected from insulin convulsions acts as a criterion of gluco-corticoid activity

C. MUSCULAR ACTIVITY TESTS:

(1) SWIMMING TEST (*Gaarenstroom, Waterman and Laqueur*, 1937). Two days after adrenalectomy, rats (60 gm.) are given a single injection of the compound to be tested. The "swimming time" (period during which they can swim when placed in water) is recorded before the injection and on the following two days The response is "positive" when the swimming time is doubled, "half positive" when it remains the same on the fourth as on the second day of treatment, and "negative" when it decreases.

(2) EVERSE AND DE FREMERY TEST (*1932*). Adrenalectomized rats are tied down under ether anesthesia, so that only the left hind leg can move at the ankle joint. Short electrical stimuli are applied to this limb and the tetanic contractions of the gastrocnemius muscle are recorded. Improvement in the recovery of the fatigued muscle (due to four, daily injections given prior to the test), is used as a criterion and the unit is defined as the minimum daily effective dose.

(3) INGLE'S MUSCULAR ACTIVITY TESTS (*1936-1942*). Rats are subjected to work one hour after adrenalectomy. The gastrocnemius muscle is exposed under light phenobarbital anesthesia, weighted by 10 gm., and stimulated by repeated faradic stimuli for 24 hours or until fatigue or death ensues. There are several variants of this test but usually the unit is defined as the work equivalent of two 0.2 mg. doses of Kendall's cpd. "E".

D. TESTS FOR MINERALO-CORTICOID ACTIVITY

It is known that corticoids decrease the blood potassium and cause sodium and chloride retention in adrenalectomized and, to a lesser extent, even in intact animals. Furthermore, prolonged administration of mineralo-corticoids causes nephrosclerosis in various animals, intact chicks, during the first few days of their lives being particularly sensitive to this activity. None of these reactions have been fully developed as indices for the accurate bioassay of mineralo-corticoid activity, but presumably they could be used for such purposes.

The increased resistance of adrenalectomized animals to potassium or even the above mentioned "water intoxication test" probably also depend, at least partly, upon mineralo-corticoid potency.

PHARMACOLOGY OF ADRENALINE DERIVATIVES

The most important pharmacologic properties of the principle adrenaline

sional occurrence of accessory adrenal cortices in the gonads. The unit may also be defined in different ways, but *now that pure crystalline corticoids are* available, it is best to express the potency of the unknown preparation in *comparison with that of a known* standard substance, such as desoxycorticosterone acetate, corticosterone or *dehydrocorticosterone.*

CARTLAND AND KUIZENGA (1936) define their rat unit as "the minimum daily dose of a substance which, administered by daily, single, subcutaneous injections, for 20 days, to four-week-old male rats (50 to 60 gm.), is enough to protect at least 80% of the rats and produce an average growth of at least 20 gm. per rat, per 20 days."

THE COLD TEST (*Selye and Schenker, 1938*), as many of its modifications, is based upon the fact that adrenalectomized rats are extremely sensitive to various types of non-specific damage, unless they are protected by life-maintaining corticoids. *Instead of cold,* which is used as a non-specific damage in this particular technic, other damag*ing agents (histamine, potassium, bac*terial toxins, vaccines), may also be employed, but in our experience, cold gave the most uniform results. — Male or female adrenalectomized rats (45 gm. *body weight) are placed in a refrig*erator (temperature −5° to +2° C) 24 hours after adrenalectomy and henceforth given no food or water They receive subcutaneous injections of the solution to be tested, at 0, 3, 4, 6 hours, during exposure to cold The unit is defined as "the minimum amount which *suffices to maintain alive 6 of* 9 adrenalectomized rats, when 6 of 9 untreated, adrenalectomized controls are dead." Instead of the four injections, a single subcutaneous dose, at the beginning of exposure to cold, or even oral administration of the compound (by stomach tube) at that time, are recommended; the former for slowly acting substances, the latter for solutions containing contaminants, which would not be tolerated parenterally. For greater *reliability*, larger groups of animals should be used, to compensate for individual variability in resistance to cold. The advantage of the technic is its great simplicity and sensitivity. It detects very active corticoids (e.g., *corticosterone) in doses of 12-15γ per* animal.

WATER INTOXICATION TEST *(Eversole et al. 1940). Male rats are fasted* for a period of 12 hours, beginning 17 hours after adrenalectomy, then given distilled water in an amount corresponding to 6% of their body weight. This is administered by gavage, in five, hourly portions. Urine volumes are measured at intervals of 24 hours. The technic of hormone administration is variable but in general, it is best to express the results in comparison with a known standard. The criteria are, survival during this time and excretion of more than 90% of the administered water within 11 hours.

B TESTS FOR GLUCO-CORTICOID ACTIVITY.

(1) DIABETOGENIC TEST ON INTACT RATS (*Ingle*, 1941). Rats are forcefed with high carbohydrate diets and injected with the substance to be tested. The criteria are the blood and urine glucose levels, urinary nitrogen excretion and tissue glycogen levels Glucocorticoid compounds cause glycogen deposition, hyperglycemia and glycosuria.

(2) DIABETOGENIC TESTS ON PARTIALLY PANCREATECTOMIZED RATS (*Ingle, 1941*). Daily injection of glucocorticoids causes diabetes, even if the pancreatic remnant would otherwise suffice to maintain a normal metabolism

(3) LIVER GLYCOGEN DEPOSITION TEST (*Reinecke and Kendall, 1942; Dorfman et al. 1946; Venning et al. 1946, Dobriner et al. 1946*) In the

batting allergic rhinitis, sinusitis or simple, acute coryza. For *intranasal* application, oily solutions are preferable because of their delayed effects Certain adrenaline derivatives (ephedrine, benzedrine) are often preferred for topical application, in respiratory and nasal disturbances, because (unlike adrenaline) their vasoconstrictor effect is not followed by a second phase of congestion and because their action is more prolonged. Yet it is claimed that adrenaline has the advantage of causing less local irritation.

By virtue of its vasoconstrictor action, adrenaline decreases the absorption of LOCAL ANESTHETICS and thus prolongs their effect, diminishes their systemic toxicity and decreases the likelihood of hemorrhage due to the surgical interventions, for which the local anesthetics are given For this purpose the hormone is added to solutions of such compounds (e.g., procaine and its derivatives, which unlike cocaine, lack vasoconstrictor potency), in concentrations of 1 100,000 to 1 20,000

Corticoids. — At the present time, only DESOXYCORTICOSTERONE ACETATE is commercially available in pure form for clinical use. It is distributed in oil solution, in sterile ampules for subcutaneous or intramuscular injection. It can also be administered in the form of sublingual drops of a propylene glycol solution, since it is effectively absorbed from the oral mucosa. This method of administration, as well as the subcutaneous implantation of compressed crystal-pellets (which are very slowly absorbed), save the patient the inconvenience of innumerable injections The absorption rate is somewhat unpredictable, however, especially in the event of sublingual administration

AQUEOUS EXTRACTS, or partially purified mixtures of the various cortical steroids, are prepared from cattle or pig adrenals and distributed in sterile ampules for subcutaneous or intramuscular *injections*. These preparations have the advantage of possessing marked gluco-corticoid activity and are used if an especially rapid action is desired (e.g., addisonian crisis). Solutions of cortical extract concentrates in oil (for subcutaneous or intramuscular injection), are used when prolonged action is desirable. All these preparations are standardized in biologic units or in mg. equivalents of pure corticoids

Additional pure corticoid steroids will probably soon be commercially available, especially DEHYDROCORTICOSTERONE, which can now be made by partial synthesis and has the advantage of gluco-corticoid potency as judged by animal experiments. It must be admitted however, that clinically, dehydrocorticosterone proved rather inactive. Perhaps higher doses or other gluco-corticoids will prove more satisfactory.

Corticoids are much less potent *by mouth* than parenterally, yet they can perhaps be given orally if sufficiently large quantities are made available. A CHARCOAL ADSORBATE of corticoids, prepared from impure extracts, has been advocated for oral use, since the intestinal juices elute the activity from the charcoal and make it available to the patient.

Intravenous administration of cortical extracts is necessary only in emergencies such as addisonian crises or shock.

ACTIVATION AND INACTIVATION

A number of drugs may influence the action of adrenaline by increasing or decreasing some, or all, of its activities

Drugs which antagonize the actions of adrenaline and of sympathetic stimulation are generally referred to as "adrenolytic" and "sympatholytic" substances, respectively (*Bacq and Fredericq*)

derivatives have been mentioned on pp. 96-98.

MODE OF ADMINISTRATION

Adrenaline. — The offical U.S.P. DESIGNATION for adrenaline is "epinephrine" while the B.P. designation is "adrenaline." Unfortunately, certain terms such as "adrenaline" and "suprarenin," are commonly in use for the designation of the hormone, although they have been trade-marked by commercial companies.

The free hormone is rather insoluble in most solvents, hence the commonly employed PREPARATIONS contain it as water-soluble salts, especially the hydrochloride. Adrenaline is sensitive to the action of oxidizing agents, particularly in alkaline solution. Light enhances the oxidation of the hormone to pink, violet and eventually brown, inactive oxidation products; to prevent this it is preserved in dark, air-tight, bottles.

The dextrorotatory isomer is only about 1/18 as active as the levorotatory (natural) hormone. Hence, only the latter is employed for clinical purposes. The official U.S.P. "solution of epinephrine hydrochloride" or the B.P. "solution of adrenaline hydrochloride" are 1:1,000 sterile solutions of the compound in distilled water. They are nearly colorless and keep well if a preservative is added (for instance, 0.5% chlorbutanol or sodium bisulfite). The solution will stand a short period of boiling if necessary.

Usually it is administered INTRAMUSCULARLY or SUBCUTANEOUSLY as the standard aqueous (1:1,000) solution, in doses of 0.2-0.5 cc. Unfortunately, the resulting local ischemia makes the tissues ideal media for anaerobic, spore-bearing, microorganisms. Following subcutaneous injection of contaminated adrenaline solutions "epidemics" of tetanus have occurred in hospitals Spores may also be introduced, inadvertently, during injection. Such complications are less common after intramuscular than following subcutaneous injections, hence the former are preferred.

Adrenaline in oil (0.2%) solution can be given in doses of 0.75-1.5 cc. subcutaneously or intramuscularly, because of the slower absorption rate.

For delayed action, the comparatively insoluble, free base is distributed in the form of a suspension in oil (2.0 mg. per cc.) for intramuscular or subcutaneous injection. This is sometimes referred to as "slow epinephrine."

It is especially useful for instance, in inoperable hyperinsulinism and asthma.

Adrenaline is extraordinarly inactive BY MOUTH, presumably because most of the hormone is inactivated in the gastrointestinal tract, or during its passage through the liver.

INTRAVENOUS or INTRACARDIAC injection of the drug is dangerous and recommended only in cases of extreme emergency (e.g., for resuscitation). It is rarely necessary to give more than 0.25 mg. and even this should be injected very slowly.

A 1.0% solution of adrenaline hydrochloride in 0.9% sodium chloride is used for INHALATION, especially in asthmatic patients during an attack. For this purpose, it may also be given in a 1:1,000 glycerin solution. All-glass nebulizers should be used to avoid destruction of the hormone due to contact with metal.

Ointments (1:1,000 in petrolatum) and suppositories (1:1,000 in cacao butter) are used for the direct application of adrenaline to the SKIN or rectal MUCOUS MEMBRANE. The standard 1:1,000 aqueous solution is employed on other mucous membranes or wound surfaces, where the vasoconstrictor action of the hormone is desirable, to stop hemorrhage. This vasoconstrictor effect is particularly useful in com-

of certain receptors (pupil, heart), causes a somewhat similar sensitization perhaps because, in the absence of constant nervous stimulation, the sympathomimetic substances tend to accumulate in the denervated or cocainized structures. It will be recalled that denervation also raises the sensitivity to acetylcholine, allegedly because its normal, continuous destruction by choline-esterase is deranged ("Law of denervation").

SENSITIZATION AND DESENSITIZATION

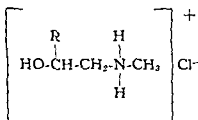
There is no convincing evidence to show that, upon repeated administration of either adrenaline or corticoids, the organism acquires any great increase or decrease in its sensitivity to these hormones. It must be kept in mind that adrenaline has a brief action and is rapidly destroyed or eliminated, hence even repeated daily injections will not result in a CUMULATIVE EFFECT The corticoids on the other hand are generally more slowly acting and the effect of many daily, or even less frequent, injections may eventually result in a cumulative action (e.g. hypertension, kidney damage).

Some degree of ADAPTATION to adrenaline has been demonstrated, however, inasmuch as after repeated injections of small amounts, the resistance to subsequent fatal doses tends to increase. Similarly, it has been found that following repeated intraperitoneal administration of desoxycorticosterone acetate, the dose necessary to produce general anesthesia, rises. The thymus atrophy of rats, chronically treated with subcutaneous injections of desoxycorticosterone, also tends to be transitory. Indeed, there appears to be a reversal of this effect after several weeks. These are not examples of true adaptation to the hormone itself, since the organism resistant to the anesthetic or the antithymus effect of the compound, indefinitely retains its sensitivity to most other effects (hypochloremia, compensatory adrenal atrophy, etc). In such instances it is preferable to speak of selective "end-organ resistance." Bioassay of the blood of these animals has shown, furthermore, that the adaptation is not due to antihormone formation; indeed, there is little evidence of true anti-hormone production against any steroid compound.

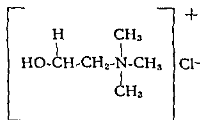
THEORIES CONCERNING THE ADRENAL HORMONES

Biogenesis of Adrenaline. — Attention has been called to the similarity between the chemical structure of choline and the side chain of adrenaline. This fact, and the presence of large quantities of choline in the adrenals, led to the supposition that the latter compound may play a rôle in the biogenesis of adrenaline.

This similarity is especially striking if choline chloride (the form in which choline exists in tissues) is compared with adrenaline hydrochloride, writing their formulae in accordance with current concepts concerning the valence of their nitrogen



Adrenaline hydrochloride

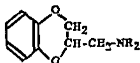


Choline chloride

ERGOTOXINE or ERGOTAMINE do not affect the inhibitory actions of the hormone (e.g., intestinal relaxation, vasodilatation), but inhibit the excitatory effects (e.g., motor and secretory stimulation). *In this respect, the ergot* alkaloids influence the actions of adrenaline, and those of sympathetic stimulation, in the same manner, that is, they are both adrenolytic and sympatholytic.

As a result of this selective inhibition of excitatory responses, some of the *actions of the hormone appear to be* inverted following pretreatment with ergot. This phenomenon is usually referred to as "ADRENALINE REVERSAL." Thus, the hormone causes a drop in blood pressure and expansion of amphibian melanophores following such pretreatment, while normally, the *pressor and melanophore-contracting actions* prevail. The hyperglycemic effect of the hormone is likewise abolished by ergotoxine.

It has also been possible to prepare a series of interesting sympatholytic DIOXANE DERIVATIVES of the general formula:



Among these, the most important are "F933" (2-piperidinomethyl-1,4-benzodioxane), which antagonizes the augmentor responses to adrenaline, but not to sympathetic stimulation; "F883" (2-diethylaminomethyl-1,4-benzodioxane), which counteracts the augmentor responses both to adrenaline and to sympathetic stimulation and "F1081" (2-methoxy-5-iodo-phenoxyethyldiethyla*mine) which annuls* the effect of inhibitory sympathetic stimulation

In honor of *E Fourneau*, whose work led to the synthesis of these *compounds*, they are generally designated by the letter "F" and the serial number which this author assigned to them.

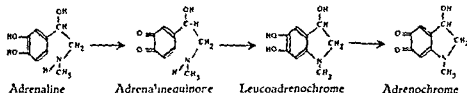
It is of special interest that certain ADRENALINE DERIVATIVES (e.g., adrenoxine), inhibit or reverse *the actions of* subsequently administered adrenaline, in those organs which are normally *excited by the hormone. Pretreatment* with other adrenaline derivatives may, on the other hand, actually increase sensitivity to the hormone.

It is not within the scope of this book to discuss all the substances *which may* antagonize adrenaline actions; it is noteworthy, however, that many other compounds *exhibit adrenolytic* properties, for instance yohimbine, quinine and its derivatives, cotarnine, hydrastinine, emetine, corynanthine, chelidonine, lycorine, apocodeine and hordenine. Indeed, even a phenomenon of so-called "DOUBLE REVERSAL" has been observed following successive administration of *ergotamine and corynanthine (both of* which cause adrenaline reversal). That is to say, adrenaline increases the blood pressure in a dog pretreated with both of these drugs, just as it does in the non-pretreated animal, although separately, each of the drugs causes reversal of the pressor response to the hormone. The therapeutic possibilities of these combinations have not been adequately explored

Other drugs antagonize adrenaline actions, merely because their own pharmacologic properties happen to be opposite to those of the hormone Among these, we might mention HISTAMINE and ACETYLCHOLINE Here, we do not speak of true adrenolytic properties but merely of drug antagonism

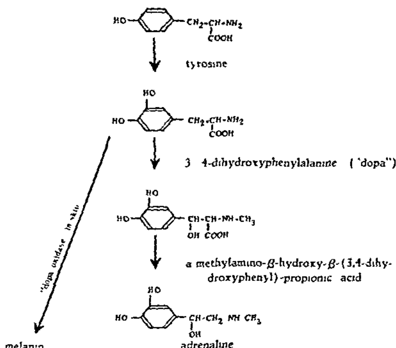
Conversely, some compounds related to adrenaline (e.g., ephedrine, thyroid hormone), may INCREASE THE RESPONSIVENESS OF CERTAIN TARGET ORGANS TO SUBSEQUENT ADRENALINE STIMULA*TION. Cocaine and* its derivatives enhance especially the vasoconstrictor, cardiac and pupillary reactions to *adrenaline. Sympathetic* denervation

of oxidizing the nucleus of adrenaline to an inactive red product "adrenochrome," which is also obtained by the enzymatic oxidation of tyrosine:

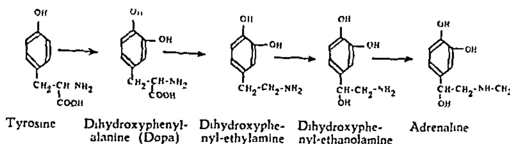


This upon further oxidation is claimed to turn into "*adrenoxine*", a substance with acetylcholine-like negative ino- and chronotropic actions. Curiously, among organ extracts only those coming from structures inhibited by adrenaline (exception · small intestine) catalyze this reaction. Still further oxidation leads again to completely inactive products. It is doubtful what rôle, if any, is played by these reactions in vivo.

Numerous workers found that partial oxidation of adrenaline leads to melanin-like brown products and concluded that the hormone participates in *pigment formation*. This is of interest in connection with the skin pigmentation characteristic of Addison's disease It has been shown (Bloch) that slices of normal skin become deeply pigmented, when immersed in a solution of 3:4-dihydroxyphenylalanine (dopa), while albino skin remains unpigmented Other allied compounds (e g., tyrosine, tryptophane, pyrogallol), fail to cause pigmentation of skin sections. It was concluded that "dopa" is a precursor of melanin which can be transformed into the latter by the enzyme "dopa-oxydase," present in the skin. This was regarded as further evidence that dopa is an intermediary in the formation of adrenaline from tyrosine. Hypocorticoidism allegedly augments the formation of melanin, at the expense of adrenaline synthesis, from dopa.



Most investigators agree, however, that the likeliest precursor of adrenaline is the amino-acid, tyrosine. The *introduction of a second -OH, into the* tyrosine molecule, has been shown to occur under the influence of the enzyme *tyrosinase (found in plants but not in animals)*; some similar mechanism may *be effective in the adrenals.* Thus, dihydroxyphenylalanine ("dopa") is formed from tyrosine, under the influence of ultraviolet light, in the presence of Fe^{++} ions or ascorbic acid. One possible pathway for the biogenesis of adrenaline would be the following :



Tyrosine   Dihydroxyphenylalanine (Dopa)   Dihydroxyphenyl-ethylamine   Dihydroxyphenyl-ethanolamine   Adrenaline

It is also claimed that slices of kidney tissue can decarboxylate tyrosine and thus form tyramine in vitro. This tyramine can then be transformed, by adrenal-medullary tissue, in vitro, into a substance giving biologic and colorimetric adrenaline reactions.

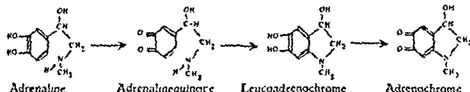
Biogenesis of the Corticoids. — This problem has been discussed in the section on The Steroids, to which the reader is referred.

Fate of Adrenaline in the Body. — It is a well-known fact that the actions *of adrenaline are extremely transitory*: even following intravenous administration of large doses, the hormone soon disappears from the blood. Neither nephrectomy nor hepatectomy significantly influence the activity of adrenaline From this it was concluded, that neither elimination through the urine nor hepatic detoxification play an important rôle in its inactivation. If adrenaline is injected into the portal vein or a peripheral artery (that is, if the hormone must pass through a capillary network before reaching the general circulation), its activity is diminished. Adrenaline is also inactivated, for instance, by repeated passage through a perfused frog-leg preparation. It appears that the hormone is DETOXIFIED IN VARIOUS TISSUES, its inactivation not being limited to any one organ. This is hardly unexpected in view of the great lability of the hormone; however, urinary elimination of adrenaline metabolites, also plays an important rôle, especially *if very large quantities are administered.* Thus, it was shown that in rabbits much of the adrenaline injected reappears in the urine as protocatechuic acid. In man, adrenaline sulphate can be recovered from the urine following its ingestion (the yield being about 70% of the hormone given). This pharmacologically inert adrenaline ester can be reconverted into the active hormone, by hydrolysis.

Probably the most important method for the inactivation of adrenaline in the body is its oxidation. In vitro *experiments indicate that* AMINE-OXIDASE (tyraminase, adrenaline oxidase) can split the side chain at the amino group *with the formation of an aromatic* aldehyde having no pressor action (oxidative deamination)

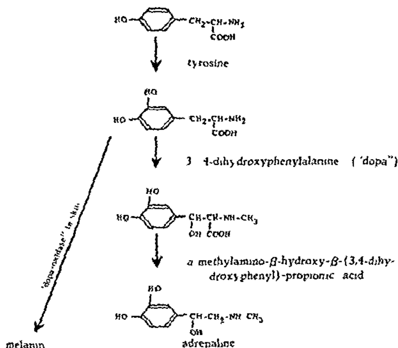
Other enzymes, the POLYPHENOL OXIDASES (of potatoes and mushrooms, catechol oxidase, cytochrome-cytochrome system, peroxidase) are capable

of oxidizing the nucleus of adrenaline to an inactive red product "adrenochrome," which is also obtained by the enzymatic oxidation of tyrosine.



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Fate of Corticoids in the Body. — (See also: The Steroids.) It has been shown that partial hepatectomy greatly prolongs and increases the activity of various corticoid hormones, and that the latter are less active when administered through the portal circulation than when introduced into the systemic blood circuit. We may therefore conclude that the liver plays an important (though probably not the sole) part, in the inactivation of corticoids. Following administration of large doses of desoxycorticosterone acetate, there is a small increase in urinary pregnanediol elimination but this can only account for a minute fraction of the hormone destruction. Probably most of the exogenous or endogenous corticoids are completely oxidized or transformed into inactive steroid derivatives. In any case no significant amount of corticoids appear in the urine in the form in which they are present in the adrenals.

Mechanism of Adrenaline Action. — Since a striking similarity exists between the effects of adrenaline and of sympathetic nerve stimulation, it has been assumed that the hormone acts through SYMPATHETIC NERVE ENDINGS This view was apparently corroborated by the observation that, unlike other vessels, those of the placenta, which are not innervated, do not respond to adrenaline. However, in chick embryos, adrenaline inhibits the rhythmic contractions of the amnion, which is not innervated, it also causes contraction of blood vessels, in chick embryos, before they are innervated: it accelerates the rate of the, not as yet innervated, heart in fish embryos or in nerveless tissue cultures of cardiac muscle cells Denervated organs, far from being insensitive, become actually hypersensitive to the action of adrenaline Topical application of the hormone, to sympathetic or sensory nerves or sympathetic ganglia, remains without effect; nicotine, which paralyzes sympathetic ganglion cells, does not inhibit the action of adrenaline. All these observations merely indicate, however, that the hormone does not necessarily act through the intermediary of nerves, without implying that it cannot influence the nervous system. The old concept, that adrenaline can migrate through the nerves (*neurocriny*), *has not received* confirmation.

As regards the CHEMICAL MECHANISM of adrenaline action, it has been *found that calcium and potassium ions* are indispensable for certain actions of the hormone, but their exact rôle has not been determined.

*It will be kept in mind that adren*aline acts as a drug with gradient action ("Potenzialgift"), since it influences the heart and blood vessels, not only at the time when it enters into their substance, but also when it leaves them ("Auswaschphanomen").

Mechanism of Corticoid Hormone Action. — It is most probable that the GLUCO-CORTICOIDS owe most of their effects, primarily, to gluconeogenesis. These compounds facilitate the conversion of non-sugars (mainly proteins) into carbohydrates and thus replenish the glycogen stores of the body, even in the fasting animal.

The MINERALO-CORTICOIDS facilitate the elimination of potassium through the kidneys, but, at the same time, cause retention of sodium, chloride and water in the tissues Since nephrectomy does not completely abolish the effect of mineralo-corticoids upon electrolyte and water distribution, it must be assumed that their action is not solely due to an influence upon urine secretion. Their marked effect upon capillary permeability and tissue affinity for *water and electrolytes probably plays* an important, though meanwhile cryptic, rôle in the mechanism of their action.

We are entirely ignorant of the mechanism through which the corticoids — like so many other steroids — exert their general ANESTHETIC EFFECT in acute experiments. It is reasonable to assume, however, that the periodic paralysis induced, especially in dogs, by chronic desoxycorticosterone acetate treatment, is the result of the replacement of muscle potassium by sodium. It has been shown that potassium administration and sodium withdrawal antagonize this action of desoxycorticosterone acetate and that a marked lowering of the blood and muscle potassium, together with an increase in muscle sodium, accompany the motor disturbances

The LIFE-MAINTAINING ACTION of corticoids, in adrenal insufficiency, is probably due to a combination of effects. The diverse actions of the corticoids upon metabolism, circulation, heat regulation, etc., are all indispensable for the maintenance of life and especially for the acquisition of adaptation to changes in the external or internal environment of the body. It appears that the corticoids are particularly useful during the *process of adaptation* but become relatively dispensable for the *performance* of functions to which inurement has already been acquired. Thus, pretreatment with cold, drugs or exposure to muscular exercise, *prior* to adrenalectomy, endow the organism with a resistance, which is largely maintained even following subsequent removal of the adrenal glands. Any of these damaging agents is extremely noxious to unadapted adrenalectomized animals This led to the concept that it is, not the actual performance of special functions, but, the acquisition of inurement, which requires specially large quantities of corticoid hormones Since continuous adaptation to changes in our external and internal environnement is the most characteristic feature of life, the great biologic importance of corticoids, for all vital processes, is readily understandable.

Among the EARLIER THEORIES of corticoid action, the following deserve brief mention .

(1) *The Detoxification Theory* (Brown-Séquard, 1890, Langlois, 1893; Riml, 1938). According to this concept, the cells of the adrenals remove toxic substances from the blood that passes through the glands In this original formulation, the theory has been abandoned, after it became known that *adrenalectomized animals are maintained by extracts of the cortex.*

A later modification of the same theory, postulates that the cortical hormones endow extra-adrenal cells with special detoxifying functions and that, in the absence of corticoids, the organism is poisoned by endogenous, toxic metabolites. This formulation of the detoxification theory is not incompatible with our views (e.g., the adaptation syndrome theory), but up to the present it has not been possible to demonstrate the accumulation of any hypothetic, toxic metabolites, in the tissues of adrenalectomized animals.

(2) *The Acidosis Theory* (*Swingle*, 1927), postulated that the manifestations of adrenal insufficiency are secondary to the development of a severe acidosis This view has been abandoned

(3) *The Respiratory Theory* (*Bornstein and Holm*, 1923). Hyperpnea is a rather characteristic manifestation in the terminal stages of adrenal insufficiency The resulting decrease in the CO_2 tension of alveolar air and blood were regarded as the cause of the adrenal deficiency syndrome, but it was subsequently shown that animals kept in a high CO_2 atmosphere, in which a loss of blood CO_2 is impossible, still develop characteristic adrenal-insufficiency symptoms.

(4) *The Theory of Temperature Regulation* (*Sajous*, 1925), regarded the maintenance of body temperature as the main function of the adrenals. This view is incompatible with the fact that adrenal insufficiency develops even if the body temperature is artificially maintained.

(5) *The General Tissue Hormone Theory* (*Hartman* et al. 1932), regarded the corticoids as "general tissue hormones," necessary for the functions of all tissues. While this is undoubtedly correct, it is merely a statement of a fact rather than an explanation.

(6) *The Carbohydrate Metabolism Theory* (*Britton and Silvette*, 1932), regards all the manifestations of cortical insufficiency as secondary to hypoglycemia. However, adrenalectomized dogs may not show any decrease in blood sugar, nor be improved by glucose administration, at the time cortical insufficiency symptoms are manifest. Furthermore, pancreatectomy fails to counteract all the manifestations of cortical insufficiency, even if it raises the blood sugar concentration

(7) *The Circulatory Theory* (*Kellaway and Cowell*, 1923), considers the hemoconcentration, and the increased capillary permeability, as the basic disturbances in cortical insufficiency. This would account for an inability to maintain consumed fluid in the circulation, which in turn would cause all other symptoms. However, prolonged withdrawal of food and water causes circulatory disturbances similar to those seen after adrenalectomy, without eliciting a typical adrenal insufficiency syndrome; conversely, continuous fluid infusions do not considerably prolong the life of adrenalectomized animals, even though the blood volume is restored.

(8) *The Potassium Intoxication Theory* (*Zwemer and Truszkowski*, 1936), was based upon the observation that the potassium concentration of the plasma runs roughly parallel with the manifestations of adrenal-cortical deficiency, in suprarenalectomized animals Toxic doses of potassium salts imitate certain manifestations of suprarenal insufficiency and adrenalectomized animals are extraordinarily sensitive to potassium ions. Corticoids restore the blood potassium to normal and raise the potassium resistance of adrenalectomized animals. It was concluded that a disturbance in potassium metabolism is the primary cause of adrenal insufficiency and that the changes in water distribution, sugar metabolism and the balance of sodium and chloride, are all secondary phenomena. It has been shown, however, that on certain diets, adrenalectomy causes no changes in serum potassium, yet it induces a typical deficiency syndrome. Furthermore, animals receiving large doses of potassium acquire a resistance to it, which persists even following subsequent adrenalectomy, although the blood potassium rises far above the level usually seen at death from cortical insufficiency.

(9) *The Histamine Intoxication Theory* (*Lucas*, 1926), assumed that endogenous intoxication with histamine is the cause of cortical insufficiency, but it has not been possible to demonstrate a constant increase in blood or tissue histamine following suprarenalectomy It is true that the histamine resistance of adrenalectomized animals is decreased, but adrenaline appears to be even more potent than the corticoids in restoring histamine resistance to normal. In any case, a decreased resistance to histamine would not be significant since, in the absence of the adrenals, resistance to almost all toxic substances is diminished

(10) *The Flavine Theory* (*Verzár*, 1936), was based on the claim that cortical extracts are unable to maintain adrenalectomized rats alive, if the diet is deprived of flavine — provitamin B_2

It has also been stated that flavine-phosphate maintains the life of adrenalectomized animals just as well as cortical extracts, while lactoflavine is inactive. It was concluded that the function of the corticoids is to enable the organism to combine flavine with phosphate and that all symptoms of adrenal deficiency result from a breakdown of this mechanism. Subsequent work failed to confirm the observations upon which this theory was based.

(11) *The Sodium and Chloride Deficiency Theory* (*Harrop* et al. 1933) regards the derangement in NaCl metabolism, as the basic cause of the adrenal insufficiency syndrome. In the adrenalectomized dog, the hypochloremia and hyponatremia run parallel with the increased loss of NaCl through the urine, since the loss of these electrolytes causes dehydration, due to the accompanying loss of extracellular tissue water. Administration of NaCl improves the condition of adrenalectomized animals, if it results in NaCl retention. It has also been found that, even in intact animals, sodium deficiency simulates the manifestations of adrenal insufficiency However, in animals recovering from adrenal insufficiency, due to cortical extract administration, the chloremia and natremia may remain low, in spite of obvious clinical improvement, if electrolyte deficient diets are given. The disappearance of the symptoms is apparently due to a shift of fluids from the tissues into the blood and this shift may occur in spite of a low serum sodium and chloride concentration The loss of NaCl through the urine is likewise not an essential prerequisite for the development of cortical insufficiency: adrenalectomized dogs can be maintained with cortical extracts, even on diets so poor in NaCl that subsequent withdrawal of the cortin causes no further loss of these electrolytes through the urine

It is obvious that any of the metabolic disturbances characteristic of adrenal insufficiency, if they are sufficiently severe, can be the immediate cause of death. Thus, hypoglycemia, (especially in animals fasted or kept on low carbohydrate intake), decrease in body temperature (especially in animals kept in cold surroundings), potassium intoxication (especially in animals receiving high doses of this ion), NaCl deprivation (especially on diets containing inadequate amounts of salt) can all be regarded as the most important disturbance in individual cases. Their fundamental rôle, in the insufficiency syndrome, is clearly demonstrated by the great improvement seen following administration of sugar, heat, sodium chloride, etc., under special circumstances. It is also evident that a severe disturbance, in any of these functions, secondarily aggravates the condition of adrenal insufficiency thus adversely influencing other functions, while correction of any one derangement exerts a beneficial action upon the organism as a whole. This does not mean that any one of the above mentioned changes is necessarily and always the cause of the entire deficiency syndrome, but merely that it can, under certain circumstances, become the weakest point, and hence the limiting factor, in the body's effort to survive.

Different Kinds of Adrenaline. — It has been claimed that adrenaline exists in the medulla partly in the form of a comparatively less active, side-chain-substitution product, designated as "PRO-ADRENALINE" or "VIRTUAL ADRENALINE." Even mere drying of the glands (in vacuo, over sulfuric acid) splits the substituent off the molecule and causes a marked increase in hormone activity

Many other observations suggest that adrenaline may exist in the gland in a combined form attached to lipids,

ascorbic acid, or protein (*"latent adrenaline"*) or lactic acid (*"lactyladrenaline"*). None of these adrenaline modifications have definitely been proven to play a physiologic rôle. Even if adrenaline were present in some *esterified or otherwise masked form*, there is no reason to believe, that this would cause a qualitative change in its pharmacologic properties, and thus result in a physiologically different kind of adrenaline.

Whether SYMPATHIN is essentially different from adrenaline is still much debated, although the liberation of an adrenergic substance by certain sympathetic nerves is no longer in doubt

The action of some organs is inhibited (e g., muscular relaxation), while that of others is stimulated (e g, muscular contraction), by excitation of their adrenergic nerves *Cannon and Rosenblueth* (1933) claimed that the sympathin liberated by excitatory adrenergic nerves, exerts an excitatory effect on distant organs, while the sympathin, produced by inhibitory adrenergic nerves, acts as an inhibitor upon the organs to which it is carried through the blood stream. These facts were interpreted as follows The nervous stimulation liberates a substance similar to adrenaline, which has both inhibitory and excitatory effects (substance "M") This compound is transformed into a pure excitatory substance "sympathin E" (E for excitatory) in organs in which it causes excitation and into a purely inhibitory substance *"sympathin I"* (I for inhibitory) in organs in which it causes inhibition Both these substances *are then carried to distant organs* through the blood Stimulation of the nerves of the liver, heart, extremities or tail, have marked excitatory effects but only very weak inhibitory actions on distant organs, hence they distinctly differ from adrenaline. Furthermore, in ergotoxin-treated cats, the pressor effects of adrenaline is reversed into a depressor action, while stimulation of the *hepatic nerves still increases* the blood pressure It has also been shown that stimulation of hepatic nerves has no effect upon the denervated iris of the cat, while stimulation of the cardiac sympathetic causes mydriasis

Tyrosinase or catechol-oxydase pretreatment changes the pharmacologic action of heart perfusates, obtained after sympathetic stimulation, so that instead of exerting an adrenaline-like effect, their action becomes purely inhibitory These enzymes are also known to oxidize the hormone to adrenoxine, a substance with acetylcholine-like negative ino- and chronotropic actions This *adrenoxine* (or some similar adrenaline derivative) could be "sympathin I". In this connection, the resemblance between the side chain of adrenaline and choline (a depressor substance), should also be recalled On the other hand, "sympathin E" has been considered to be identical with *arterenol*, which possesses the pharmacologic properties of the hypothetic excitatory substance.

In any case *Cannon and Rosenblueth* never actually proved the existence of a purely excitatory or inhibitory sympathin They merely showed that during the humoral transmission of sympathetic impulses, more excitatory and less inhibitory effects are noted than after injection of adrenaline. Furthermore, contrary to what the theory postulates, the perfusate (or venous blood) of an inhibited organ fails to produce inhibitory responses in organs which are normally excited by sympathetic stimulation or vice versa

It is probable that "sympathin-I" is adrenaline, "sympathin-E" is nor-adrenaline (arterenol). However, until this is definitely established, it may be best to use the designation "sympathin-N" ("N" for Nor-adrenaline) instead of "sympathin-E", and "sympathin-A" ("A" for Adrenaline) instead of "sympathin-I". This would emphasize, without definitely accepting, the probable identity of these two compounds with nor-adrenaline and adrenaline respectively (*v. Euler, Bacq*).

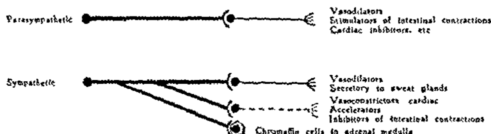
The above interpretation is mainly *based upon the finding that extracts of* various animal (mammalian) tissues, especially nerves, contain an amine which possesses nor-adrenaline-like actions, while other tissues (e.g., human coronary arteries and nerves) contain a compound with more adrenaline-like actions Indeed, certain cells (e g., those of the abdominal ganglion of annelids or the frog's heart) appear to produce adrenaline itself.

Perhaps many tissues can synthesize aminated derivatives of catechol and the synthesis of adrenaline goes through arterenol; in other words, the methylation of the nitrogen would be the last step in the synthesis If this would fail

to occur in certain tissues, arterenol would be the end-product (*Bacq*)

In connection with the humoral transmission of adrenergic stimuli, it is also noteworthy that *acetylcholine* is the humoral agent responsible for the transmission, not only of all preganglionic, and postganglionic parasympathetic impulses, but also, of all preganglionic, and some postganglionic, sympathetic stimuli, as indicated by the following diagram:

FIGURE 1



Schematic drawing illustrating distribution of cholinergic and adrenergic fibers Heavy lines, preganglionic, thin lines, postganglionic, interrupted lines, adrenergic: solid lines, cholinergic

Different Kinds of Corticoids. — The steroids isolated from the adrenal cortex have been discussed in the section dealing with "The Steroids." In addition to the fully characterized adrenal steroids, there are probably several others, whose chemical structure is not yet established. Thus, in the amorphous material, which remains after isolation of the known members from the adrenal steroid fraction, there appear to be compounds of high physiologic potency which exert gluco-corticoid and mineralo-corticoid actions. Desoxycorticosterone does not appear to occur in the normal adrenal, except perhaps in traces.

Among the possible cortical hormones, whose existence is still in doubt, we might mention "CORTILACTIN" (*Hartman* et al. 1933), a compound supposedly present in adrenal extracts and necessary for the maintenance of lactation following adrenalectomy. It has also been stated that cortical extracts possess GONADOTROPHIC activity. It is possible that these effects are not due to separate hormones, but to some of the known adrenal steroids, or synergistic combinations of these. The existence of an ASCORBIC ACID SUBSTITUTED CORTICOID has also been postulated, but not definitely proven.

It is not yet known IN WHAT FORM CORTICOIDS CIRCULATE IN THE BLOOD. Since they are rather insoluble in aqueous media, it is probable that they form water-soluble esters or are bound to protein

EXPERIMENTAL PHYSIOLOGY OF THE ADRENALS

EXPLANTATION OF THE ADRENALS

The cells of the adrenal cortex, unlike those of the medulla, grow quite well in tissue cultures. Perfusion experiments with whole adrenals also yield many interesting results, especially as regards the effect of various substances (which can be added to the perfusion fluid) upon adrenaline secretion, in vitro. It is noteworthy, furthermore, that the oxygen consumption of the perfused adrenal is extraordinarily high and is further increased by the addition of adrenaline to the perfusion

ascorbic acid, or protein (*"latent adrenaline"*) or lactic acid (*"lactyladrenaline"*). None of these adrenaline modifications have definitely been *proven to play a physiologic rôle. Even* if adrenaline were present in some esterified or otherwise masked form, there is no reason to believe, that this would cause a qualitative change in its pharmacologic properties, and thus result in a physiologically different kind of adrenaline.

Whether SYMPATHIN is essentially different from adrenaline is still much debated, although the liberation of an adrenergic substance by certain sympathetic nerves is no longer in doubt

The action of some organs is inhibited (e g, muscular relaxation), while that of others is stimulated (e g, muscular contraction), by excitation of their adrenergic nerves *Cannon and Rosenblueth* (1933) claimed that the sympathin liberated by excitatory adrenergic nerves, exerts an excitatory effect on distant organs, while the sympathin, produced by inhibitory adrenergic nerves, acts as an inhibitor upon the organs to which it is carried through the blood stream These facts were interpreted as follows The nervous stimulation liberates a substance similar to adrenaline, which has both inhibitory and excitatory effects (substance "M") This compound is transformed into a *pure excitatory substance "sympathin E" (E* for excitatory) in organs in which it causes excitation and into a purely inhibitory substance *"sympathin I"* (I for inhibitory) in organs in which it causes inhibition Both these substances are then carried to distant organs through the blood Stimulation of the nerves of the liver, heart, extremities or tail, have marked excitatory effects but only very weak inhibitory actions on distant organs, hence they distinctly differ from adrenaline Furthermore, in ergotoxin-treated cats, the pressor effects of adrenaline is reversed into a depressor action, while stimulation of the hepatic nerves still increases the blood pressure It has also been shown that stimulation of hepatic nerves has no effect upon the denervated iris of the cat, while stimulation of the cardiac sympathetic causes mydriasis

Tyrosinase or catechol-oxydase pretreatment changes the pharmacologic action of heart perfusates, obtained after sympathetic stimulation, so that instead of exerting an adrenaline-like effect, their action becomes purely inhibitory These enzymes are also known to oxidize the hormone to adrenoxine, a substance with acetylcholine-like negative ino- and chronotropic actions. This *adrenoxine* (or some similar adrenaline derivative) could be "sympathin I". In this connection, the resemblance between the *side chain of adrenaline and choline* (a depressor substance), should also be recalled On the other hand, "sympathin E" has been considered to be identical with *arterenol,* which possesses the pharmacologic properties of the hypothetic excitatory substance.

In any case *Cannon and Rosenblueth* never actually proved the existence of a purely excitatory or inhibitory sympathin They merely showed that during the humoral transmission of sympathetic impulses, more excitatory and less inhibitory effects are noted than after injection of adrenaline. Furthermore, contrary to what the theory postulates, the perfusate (or venous blood) of an inhibited organ fails to produce *inhibitory responses in organs which are normally* excited by sympathetic stimulation or vice versa

It is probable that "sympathin-I" is adrenaline, "sympathin-E" is nor-adrenaline (arterenol). However, until this is definitely established, it may be best to use the designation "sympathin-N" ("N" for Nor-adrenaline) instead of "sympathin-E", and "sympathin-A" ("A" for Adrenaline) instead of "sympathin-I". This would emphasize, without definitely accepting, the probable identity of these two compounds with nor-adrenaline and adrenaline respectively (*v. Euler, Bacq*).

The above interpretation is mainly based upon the finding that extracts of various animal (mammalian) tissues, especially nerves, contain an amine which possesses nor-adrenaline-like actions, while other tissues (e.g, human coronary arteries and nerves) contain a compound with more adrenaline-like actions Indeed, certain cells (e.g., those of the abdominal ganglion of annelids or the frog's heart) *appear to* produce adrenaline itself.

Perhaps many tissues can synthesize aminated derivatives of catechol and the synthesis of adrenaline goes through arterenol; in other words, the methylation of the nitrogen would be the last step in the synthesis If this would fail

exposed by a deep incision and subsequently removed through a suction tube. Small remnants often persist, *hence the most commonly employed procedure is to transplant the adrenal tissue*, after freeing it of all visible medullary cells, taking advantage of the above mentioned fact that only cortical cells persist in grafts

For many experimental purposes, simple DENERVATION of the *adrenals* suffices to inactivate the medulla, since adrenaline production ceases almost completely following destruction of the splanchnics

EFFECTS OF ADRENALECTOMY AND TREATMENT WITH ADRENAL HORMONES

State. — ADRENALECTOMY causes the *development of a rapidly fatal insufficiency syndrome*, in *most animal* species. This is usually characterized by a rapid pulse, thirst, suppression of urine secretion, vomiting, diarrhea, muscular weakness, loss of appetite, a terminal fall in blood pressure and finally coma, *death ensuing* within *a few days*. Increased *melanin* deposition in the skin, so characteristic of adrenal insufficiency in man, is rarely seen in experimental animals and is apparently, largely dependent upon their diet.

In fish, *amphibia, reptiles and certain mammals, especially the laboratory* rat (not the wild rat, whose cortex is normally larger), the insufficiency syndrome takes a chronic course and death may not ensue until weeks after complete adrenalectomy.

The length of survival following adrenalectomy is largely dependent upon *the conditions under which the animals are kept after the operation*. High protein *diets* and exposure to any type of *stress* are especially damaging, since the corticoids play an essential rôle in gluconeogenesis from proteins, and in adaptation and resistance to diverse noxious agents On the other hand, high carbohydrate diets, and a rich supply of *sodium*, are most effective in prolonging the *life-span of animals deprived of their adrenals*. During *hibernation animals* are particularly resistant to adrenalectomy.

REMOVAL OF THE ADRENAL MEDULLA, or its inactivation by denervation, *are not followed by any very obvious manifestations of insufficiency*. Only in emergency situations is the lack of adrenaline secretion detectable. The existence of important extra-adrenal sources of adrenergic substances (sympathetic nerve endings, paraganglia) *may* explain why a *syndrome of severe* adrenal medullary insufficiency cannot be so produced

In man, ADRENALINE given in toxic doses, may produce a feeling of anxiety, *fear*, tenseness, throbbing headache, *tremor, weakness, dizziness*, palpitation and *difficulty of respiration* All these manifestations are usually transitory, yet quite alarming to the not forewarned patient. Still higher doses may produce an unduly sharp *rise in blood pressure, accompanied* by *cardiac arrhythmias, anginal pain*, and sometimes even cerebral hemorrhage or hemorrhagic lung edema. Ventricular arrhythmia, ventricular fibrillation and lung edema are the most common causes of death due to *adrenaline overdosage*. Patients with *hypertension, arteriosclerosis* (especially coronary disease) or hyperthyroidism are particularly sensitive to this hormone Individual tolerance varies, but 2 mg intravenously or 8 mg. subcutaneously, is usually fatal in normal man

CORTICOIDS *rarely produce any signs of acute overdosage*. Upon prolonged administration, however, desoxycorticosterone acetate may cause a great increase in blood volume with cardiac dilatation, hypertension and proteinuria in man and in animals. Addi-

fluid, or by stimulation of the splanchnic *nerves*.

TRANSPLANTATION OF THE ADRENALS

Although heterotransplantation of adrenal-cortical tissue is *rarely successful*, homotransplants and especially autotransplants, take quite readily in *various species, including man. Special* care should be taken to free the cortex of all traces of medulla, since adrenaline causes necrosis, not only of the chromaffin cells, but, even of adjacent cortical tissue. *A simple technic which* permits transplantation of medullary tissue, is that in which the vascular pedicle of the gland is preserved and the organ is merely transposed Otherwise *the medulla takes only in rare* cases

That the medulla usually succumbs in adrenal grafts proves of value in studies concerning the physiology of *pure cortical tissue If the adrenals are removed, freed of visible medullary tissue* and subsequently transplanted, it may be taken for granted that after some time the graft will consist of pure cortical tissue. *Even if a few medullary* cells had, accidentally, remained in the transplants they would have become necrotic.

TECHNIC OF ADRENALECTOMY

The previously mentioned fact, that in certain selachian FISH, the adrenal cortex forms an organ anatomically separate from the medulla, renders removal of this "interrenal organ" tech*nically simple.* The *intervention results* in pure cortical insufficiency, without damage to the adrenaline-producing system.

In most AMPHIBIA the adrenals are *intimately connected with the anterior* surface of the kidney and are best removed by cauterization.

In BIRDS, *adrenalectomy is particularly* difficult because of the close connections between the glands and the very friable vena cava. Here it is useful to slit the capsules of the glands and to remove their parenchyme through a glass cannula, connected with a *suction pump (similar to the* cannula used for hypophysectomy). *In order to prevent the continued* growth of small, undetectable, cortical remnants, a cotton pad soaked with *ferric chloride solution,* may be applied to the inner surface of the adrenal capsules after the operation.

In most MAMMALS, including man, the removal of the adrenals is not attended with great technical difficulties Adrenalectomy is best performed through two separate subcostal incisions, remaining in the retroperitoneal space as far as possible. The operation may be performed in one stage in the *laboratory rat* and *mouse*, which are comparatively resistant to adrenal insufficiency and in whom both adrenals are readily accessible In the *guinea pig, rabbit, wild rat, cat, dog* and *monkey* it is preferable to remove the right adrenal (which, being adherent to the liver and vena cava, is more difficult to dissect) in a first stage, *so that the animal still has functional* adrenal tissue on the left side while recovering from the operation. One or two weeks later the comparatively free left adrenal can subsequently be removed *without much surgical trauma* Before the second adrenal is removed, it is well to administer fairly high doses of corticoids, in order to prevent *acute* adrenal insufficiency during the postoperative period In view of the rich nerve and blood supply of the adrenals, it is especially important that this oper*ation be performed with impeccable* surgical technic, using blunt dissection as far as possible

SEPARATE REMOVAL OF THE MEDULLARY TISSUE is rather difficult. It can best be performed in small laboratory rodents (e.g., rat), in whom the cortex forms a regular, spheric envelope around *the medulla. The medulla is*

through the liberation of sympathin, may cause the slight residual hyperglycemia of adrenalectomized animals. Other experimental hyperglycemias and glycosurias, such as those produced by *splanchnic stimulation, theobromine, traumatic shock*, etc., are likewise prevented by adrenalectomy, indeed *the same agents which raise the* blood sugar in the normal, may decrease it in the adrenalectomized animal This is probably due to the inability of the latter to respond to stress, either with adrenaline or with gluco-corticoid secretion, which are indispensable for the production of the above-mentioned *hyperglycemias and glycosurias*

Adrenaline causes hyperglycemia, both in the normal and the adrenalectomized animal This effect depends, however, upon the presence of adequate hepatic glycogen stores, since it is due to the breakdown of liver glycogen into blood glucose The degree *and duration* of adrenaline hyperglycemia is of diagnostic value, since it gives some indication of the amount of hepatic glycogen which can be mobilized by the patient.

The tendency to develop hypoglycemia after adrenalectomy can be counteracted by the administration of *gluco-corticoids* (e.g., corticosterone) while *mineralo-corticoids* (e g , desoxycorticosterone acetate) have no *beneficial effect, except, perhaps*, by improving the general condition of the animals. Both in the adrenalectomized and in the intact animal, treatment with gluco-corticoids raise the fasting blood sugar level, presumably by transforming protein into sugar Mineralo-corticoids (e g , desoxycorticosterone) may cause such a pronounced compensatory involution of the adrenal cortex that a tendency to severe fasting-hypoglycemia ensues, presumably due to deficient endogenous gluco-corticoid formation

Insulin causes a particularly pronounced and rapid hypoglycemia in the adrenalectomized animal. This great *insulin hyper-sensitivity is probably* due to the absence of gluco-corticoids, which normally antagonize it in the intact animal There is also a mutual antagonism between the glycemic effects of adrenaline and insulin

Thyroid hormone augments the hyperglycemic action of adrenaline unless the *resulting hyperthyroidism* is so severe as to deplete the hepatic glycogen stores

The hyperglycemia and glycosuria characteristic of various types of diabetes, (e g., that produced by *pancreatectomy*), is greatly alleviated by adrenalectomy. Conversely, even partial pancreatectomy suffices to sensitize experimental animals to the diabetogenic action of gluco-corticoids

Neither *adrenaline nor* the gluco-corticoids influence the blood sugar after *hepatectomy*. This suggests that *they do not materially affect glucose* utilization or formation in extra-hepatic tissues

GLUCOSE ABSORPTION from the alimentary tract is delayed by adrenalectomy, this deficiency is restored by gluco-corticoid hormone treatment. However, the intestinal absorption of all sugars is not equally impeded by adrenal insufficiency, there being apparently most pronounced interference *with the normal, preferential, selective* absorption of certain sugars

The STORAGE OF CARBOHYDRATE is likewise largely under adrenal control. Adrenalectomy decreases glycogen storage in the liver and muscles, while mineralo-corticoid administration raises the glycogen concentration, especially in the liver. Adrenaline depletes the hepatic glycogen reserves, since it transforms glycogen into blood glucose. There is also a simultaneous diminution of muscle glycogen However, after a prolonged fast, and in

sonian individuals *appear to be more* than normally sensitive to desoxycorticosterone overdosage.

Animal experiments indicate that *chronic overdosage* with desoxycorticosterone causes sufficiently severe adrenal-cortical atrophy to produce a modified type of adrenal insufficiency, due to suppression of endogenous gluco-corticoid production. (See p. 119.)

Temperature. — ADRENALECTOMY causes a slight decrease in body temperature and a pronounced disturbance in thermoregulation, especially in animals exposed to cold. ADRENALINE *tends to raise the body temperature* slightly, while CORTICOIDS cause no noteworthy change.

Basal Metabolism. — ADRENALECTOMY causes a pronounced decrease in the metabolic rate of most animal species, to about *25-35%* below normal. At the same time the R.Q. tends to fall. The rise in B.M.R., normally produced by hypophyseal extracts or thyroid hormone, is not inhibited by adrenalectomy. Hence, these hormones do not act merely through the intermediary of the adrenals. Administration of glucose raises the low B.M.R. *and* low R.Q. of *suprarenalectomized* animals There is no reason to believe, therefore, that the adrenals are indispensable for the combustion of sugar.

ADRENALINE *raises the B.M.R.*, without exerting a consistent effect upon the R.Q. CORTICOIDS and especially cortical extracts rich in gluco-corticoids, restore *the low B.M.R. and low* R.Q. of adrenalectomized animals to normal, but exert a rather inconstant influence upon the B.M.R of intact animals

Tissue Metabolism. — It has been shown repeatedly that the metabolism of tissues, taken from ADRENALECTOMIZED animals, is impaired. Their basal oxygen consumption is diminished and the increment in oxygen uptake, which follows the addition of *various amino-acids or the* corresponding keto-acids, is subnormal. CORTICOID extracts correct these derangements.

The metabolism of various tissues is increased by ADRENALINE, especially if optimal amounts of oxygen are not available. All *these findings indicate* that the adrenals exert a direct influence upon the metabolism of tissues.

Carbohydrate Metabolism. — The *fundamental factors regulating carbohydrate metabolism* have been discussed *in the section on the* Pancreas (Experimental Physiology), to which *the reader is referred.*

THE BLOOD GLUCOSE concentration is decreased by *adrenalectomy*, especially if the experimental animal is deprived of exogenous sugar. Under optimal conditions of maintenance, that is, on a high carbohydrate, high sodium chloride intake, adrenalectomized animals (especially the rather resistant laboratory rat, in contrast to wild rats and most other species), may maintain a normal or even high blood glucose concentration. However, *fasting* or any *non-specific stress* which increases carbohydrate combustion, is likely to *elicit a fatal attack of hypoglycemia in the* adrenalectomized animal unless it receives corticoid hormone treatment. Presumably the corticoids are *indispensable for rapid gluconeogenesis* and especially for the formation of sugars from endogenous sources (body protein and fat).

The so-called piqûre diabetes, produced by surgical lesions to the floor of the fourth ventricle, is almost, but not entirely, prevented by adrenalectomy This was interpreted to mean that in addition to the sympathetic nervous connections between the floor of the fourth ventricle and the adrenal medulla (which regulate adrenaline hyperglycemia), direct nervous connections exist between the fourth ventricle and the liver The latter, perhaps

minished. Correction of these deficiencies is mainly dependent upon the administration of mineralo-corticoid hormones.

ADRENALINE induces a transitory rise in serum potassium, presumably due to discharge of K ions from various tissues (e.g., liver). This is followed by a more prolonged hypopotassemia. The fall in the inorganic phosphate content of the blood, produced by adrenaline, is apparently due to the phosphorolysis of glycogen, with the formation of glucose monophosphate.

Adrenaline may also cause marked diuresis, due to an increase of the filtration pressure in the malpighian corpuscles, occasioned by constriction of the efferent glomerular arterioles.

Desoxycorticosterone acetate and certain other CORTICOIDS cause diuresis, presumably because they interfere with the tubular reabsorption of Na and water. Under the influence of mineralo-corticoid overdosage, hypopotassemia develops and sodium tends to replace potassium in the muscles. This has been considered to be of importance in the pathogenesis of the muscular paralysis sometimes noted in dogs, monkeys and even patients, severely overdosed with desoxycorticosterone.

The effect of corticoids upon the mineral metabolism of animals, is subject to great species variations. Thus, marsupials (e.g., *opossum*) react to adrenalectomy with hyper-rather than with hypochloremia. Baby chicks appear to be especially sensitive to the edema-producing effect of desoxycorticosterone acetate and even short treatment, with relatively small doses of this steroid, suffice to produce excessive water accumulation in the connective tissue, as well as in the large body cavities

Other Metabolites. — Numerous publications have dealt with the, allegedly important, influence of the adrenals upon the metabolism of GLUTATHIONE, ASCORBIC ACID, CHOLINE etc., but it is not yet possible to draw definite conclusions from the pertinent literature.

Growth and Bone Structure. — The somatic growth of the adrenalectomized animal is inhibited. It can be restored by corticoids but not by adrenaline.

Blood. — *Adrenalectomy* causes rather inconsistent changes in the BLOOD COUNT, these being largely dependent upon the degree of accompanying hemoconcentration. Often there is lymphocytosis.

Adrenaline administration elicits a marked increase in the number of circulating erythrocytes, and a less pronounced leucocytosis, due to the fact that it causes splenic contraction and thus evacuates blood corpuscles from the spleen into the blood stream. This is of importance in connection with the emergency function of the adrenals, since it augments the oxygen capacity of the blood and improves the chances of survival in the event of a hemorrhage. It is also of diagnostic value in certain diseases (e.g., malaria, lymphogranulomatosis, lymphosarcomatosis), since adrenaline may cause the appearance in the blood of abnormal cells otherwise hidden in the spleen Adrenaline also increases the reticulocyte count presumably by eliciting a discharge of immature red cells from the bone marrow.

Overdosage with *corticoids* causes lymphopenia, presumably due to the fact that numerous lymphocytes disintegrate as do the thymocytes within the thymic reticulum. It is claimed that, from the bodies of such disintegrating white cells, γ - globulin is freed for the manufacture of immune bodies, but this is doubtful

Adrenalectomy does not markedly influence BLOOD COAGULATION but adrenaline administration accelerates it This is also of importance in con-

other conditions which cause a serious depletion of hepatic glycogen stores, adrenaline may actually raise the liver glycogen. This is due to the fact that *the lactic acid, formed by the hormone* from muscle glycogen, is reconverted into hepatic glycogen through the "Cori cycle." (See: The Pancreas.) Thus, adrenaline transforms muscle glycogen into lactic acid, the latter is converted into hepatic glycogen, which in turn is broken down into blood glucose by the same hormone.

The LACTIC ACID content of the blood and muscles tends to diminish after adrenalectomy, apparently because of decreased lactic acid formation. On the other hand, adrenaline increases the lactic acid content of the blood, due *to the above-mentioned conversion of* muscle glycogen into lactic acid.

Lipid Metabolism. — Only a few isolated facts are known concerning the effect of adrenal hormones upon lipid metabolism. The *fatty infiltration of the liver*, produced by a variety of experimental procedures (anterior-pituitary extracts, partial hepatectomy and fasting, pancreatectomy), is prevented by adrenalectomy, unless adequate corticoid treatment is administered Certain steroids of the adrenal cortex allegedly produce heavy fatty infiltration of the liver and even massive *fat deposition in various other tissues*. Chronic desoxycorticosterone acetate overdosage tends to raise the blood *cholesterol* level, especially in the presence of renal insufficiency. All this work requires further elucidation, to be useful for the understanding of the underlying metabolic changes.

The *ketonemia, and especially the ketonuria*, of experimental diabetes (pancreatectomy, anterior-pituitary extract) and of fasting are diminished, or even abolished, by adrenalectomy. Treatment with corticoids restores the ketosis under such conditions, while adrenaline does not.

Protein Metabolism. — ADRENALECTOMY seriously interferes with protein metabolism, especially in young, growing animals. It prevents the *normal apposition* of new body protein, the regeneration of tissue protein, following partial excision of certain organs (e.g., liver, kidney), and eventually, *it results in cachexia* due to the predominance of protein-catabolic processes. Adrenal deprivation appears to affect especially the utilization of certain endogenous proteins for the formation of tissues. Thus, hepatic regeneration is inhibited in the fasting, adrenalectomized rat, although it proceeds rapidly in fasting, intact controls. This is additional evidence of the preëminent rôle played by the *adrenal in adaptive processes, such as* wound healing and regeneration.

CORTICOIDS restore the nitrogen metabolism of the adrenalectomized animal to normal, but we do not yet know which type of corticoid is responsible for this effect. In severe cortical insufficiency the high N.P.N. of the blood returns to normal when corticoid therapy is instituted. Even following bilateral nephrectomy, the rise in N.P.N. and death from uremia are delayed by corticoids. This suggests an extra-renal point of attack.

It is perhaps pertinent that adrenaline decreases the blood amino-acid concentration in the intact organism. It has also been stated that corticoids increase the γ-globulin content of the blood. These globulins are important for certain serologic defence reactions.

Salt and Water Metabolism. — ADRENALECTOMY causes dehydration *of the tissues, probably with a decrease* in extracellular, and an increase in intracellular water. This is accompanied by a sharp decrease in blood sodium and chlorides with an increase in blood potassium. Simultaneously, the urinary loss of sodium and chloride is increased, while that of potassium is di-

The oxygen consumption of the heart muscle is greatly increased by adrenaline.

Chronic overdosage with MINERALO-CORTICOIDS (e.g., desoxycorticosterone) causes cardiac hypertrophy, a pronounced and prolonged rise in blood pressure, myocardial nodules (similar to those seen in rheumatic fever), as well as periarteritis nodosa, especially in the mesenteric, coronary, and brain arteries of various experimental animals. These vascular changes may cause death due to secondary thromboses and embolisms. Hypertension and focal areas of cardiac necrosis have also been observed in man, after desoxycorticosterone treatment. Diets rich in vitamins, carbohydrates and acidifying salts, but poor in protein and Na, tend to prevent all these changes.

Lymphatic System. — Most lymphatic organs, and especially the thymus, reach a physiologic maximum of development approximately at the time of puberty. In the adult man and animals, there is a certain "physiologic involution" of these organs. Adrenalectomy prevents this normal involution of the lymphatic tissue (especially of the thymus), without actually causing true hypertrophy or hyperplasia.

It is particularly noteworthy that the "accidental involution" of the thymus, produced by a variety of non-specific damaging agents (infections, intoxications, traumatic injuries, etc.), is completely prevented by adrenalectomy. Among the innumerable agents which cause thymus involution in the intact animal, only certain steroids can produce this effect following adrenalectomy. Folliculoids, testoids, corticoids and luteoids are active in this respect approximately in proportion to their folliculoid effect. (See The Steroids.) It is assumed that all other drugs and non-specific damaging agents act indirectly through the adrenals, by increasing their steroid hormone production (See: General-Adaptation-Syndrome.)

Adrenaline causes only a slight increase in the number of circulating leucocytes, presumably by discharging them from the spleen and bone marrow.

Respiratory System. — Following ADRENALINE administration, there is an initial period of *apnea* followed by an increase in the rate and depth of respiration. The apnea is probably the result of a reflex elicited by the rise in blood pressure through the pressoreceptors of the carotid sinus.

Adrenaline also exerts an inhibitory influence upon the plain musculature of the *bronchioles*. This action is of especial value in the therapy of asthma due to bronchiolar spasms.

When given in very high doses, adrenaline may cause fatal *lung edema* due to an excessive rise of pressure in the pulmonary circulation. The latter results mainly from back pressure consequent to the increased peripheral resistance in the systemic circulation.

ADRENALECTOMY exerts no specific effects upon the respiratory system: CORTICOID overdosage may, occasionally, cause pleurisy and even lung edema.

Muscles. — ADRENALECTOMY greatly diminishes muscular strength and causes ready fatiguability. This can be combatted both by adrenaline and by corticoids, but the latter are much more effective.

ADRENALINE postpones fatigue and increases work capacity above normal even in intact animals. This is somewhat reminiscent of the so-called Orbeli effect, that is, the postponement of fatigue in a muscle stimulated through its nerve, by simultaneous stimulation of the sympathetic fibers going to the muscle. Although a direct sympathetic innervation of muscles is not probable, it is believed that sympathin liberation from vascular sympathetic fibers of muscles may be responsible for this action. The fatigue-combatting effect of adrenaline is not

nection with the emergency function of the hormone: obviously, rapid coagulation of the blood is useful during emergencies, when wounds are likely to be contracted.

Cardiovascular System. — ADRENALECTOMY decreases the size of the heart and causes a fall in blood pressure. It also sensitizes animals to the hypotensive action of various drugs and damaging agents. This tendency towards a fall in blood pressure is effectively combatted by corticoids. Adrenaline produces only a temporary rise in the blood pressure of adrenalectomized animals, without really correcting the underlying deficiency The hypertension normally elicited by constriction of the renal arteries is prevented by adrenalectomy unless adequate corticoid therapy is given.

ADRENALINE, administered in moderate doses, raises the blood pressure and strengthens the heart beat of the intact animal. At the same time the pulse rate is slowed, due to a vagal reflex through the pressoreceptors of the carotid sinus and aortic nerves. The bradycardia in this case is elicited only if the blood pressure rises, not if it is kept low by bleeding. If the vagi are previously transected, or eliminated by atropinization, adrenaline increases both the rate and the strength of the heart beat.

In man, adrenaline quickens the heart rate, even without atropinization, when it is given subcutaneously in small doses.

Certain drugs, such as chloroform, increase the sensitivity of the cardiac muscle to the production of ventricular fibrillation by adrenaline It is claimed that this sensitization is due to a shortening, by the drug, of the ventricular refractory phase and accounts for many cases of sudden syncope and death in patients in whom adrenaline had been given, or suddenly discharged from the adrenal medulla, during chloroform anesthesia.

In approximately physiologic doses, adrenaline influences the various vascular territories in a different manner. The arterioles and capillaries of the mucous membranes, skin and splanchnic viscera (except the intestinal vessels), are constricted: simultaneously, the coronary vessels as well as those of the skeletal muscles and intestines are actively dilated. At these dose levels the vasoconstrictor effect predominates over the vasodilator action and a rise in blood pressure ensues In coronary diseases, the dilatation of the coronary arteries (if it occurs) is overshadowed by the other effects, so that angina results. The arteries of the brain are passively distended through the general rise in blood pressure, while the lung vessels are not particularly affected unless large doses are given which constrict them. As a result of these changes, there is a redistribution of the blood, so that more becomes available to the skeletal and cardiac muscles, at the expense of the splanchnic area and skin.

Curiously, very small doses of adrenaline may cause a fall in blood pressure, presumably because the vasodilatation in the muscles overbalances the vasoconstriction in the skin and abdominal organs. However, if the blood pressure is already low, or the animal is kept under deep anesthesia, a pressor effect may be obtained, even with very small doses of the hormone Conversely, following ergotoxin pretreatment, even large doses of adrenaline have a depressor effect, owing to the previously-mentioned phenomenon of "adrenaline reversal." Presumably the ergot alkaloids paralyze the vasoconstrictor but not the vasodilator mechanism.

Long continued administration of adrenaline causes vascular sclerosis in certain animal species, especially the rabbit

Adrenaline also stimulates SALIVARY SECRETION and (especially in the cat), elicits the production of a copious watery saliva. This is perhaps significant in connection with the emergency function of the gland, since in the cat, spitting (with an air of displeasure) is a normal defence reaction, calculated to inspire fear.

Adrenaline stimulates the GALL BLADDER musculature.

Adrenalectomy tends to cause some involution of the LIVER and PANCREAS, this may be accompanied by functional disturbances in these organs. The hormonal mechanism responsible for these actions has not been clarified, but to a large extent they can be explained on the basis of the malnutrition accompanying severe adrenal insufficiency.

Skin and Appendages. — Unlike in man, adrenalectomy usually causes no marked skin PIGMENTATION in experimental animals, although, under certain conditions, such effects have been seen.

Adrenaline contracts the melanophores of certain poikilothermic animals, for instance, the frog and horned toad. In the latter, melanophore contraction also occurs (presumably due to adrenaline liberation) when the animal is excited

The CUTANEOUS VASOCONSTRICTION mentioned above, causes pallor of the skin following administration of adrenaline. This may also be regarded as a useful emergency reaction since it diminishes the danger of hemorrhage from possible surface wounds

The ERECTOR MUSCLES of hair are also stimulated by adrenaline. This effect is responsible for the intimidating erection of the hair and feathers during emergencies in animals, as well as for the production of "goose flesh," in man.

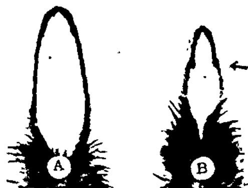
In most mammals, including man, the SWEAT GLANDS are not excited by adrenaline, although they are innervated by the sympathetic nervous system. However, in certain species (e.g., horse, sheep), the hormone stimulates sweat secretion, and even in man, there is profuse sweating during the paroxysmal attacks caused by chromaffinomas

In certain birds, adrenalectomy may cause serious disturbances in the development and especially in the pigmentation of the FEATHERS; in mammals, it leads to partial loss of HAIR. The hormonal mechanism responsible for these changes is not fully understood.

Urinary System. — ADRENALECTOMY causes no consistent morphologic changes in the urinary system, although it tends to produce a decrease in renal size and a diminution of urine production.

ADRENALINE increases diuresis due to a rise in the filtration pressure occasioned by a selective constriction of the efferent glomerular vessels. In very large doses, however, it causes anuria.

The smooth musculature of the urinary bladder is inhibited, but that of the trigonum and the ureters is excited by adrenaline.



Plumage changes after adrenalectomy. — A. Normal saddle hackles of a seabright bantam. — B. The part above the arrow grew immediately following sub-total adrenalectomy; after that, regeneration occurred.

sufficiently great, at non-toxic dose levels, to be of use in augmenting the muscular efficiency of man. Certain *adrenaline derivatives are valuable* analeptics however, because of their stimulating effect upon the central nervous system (see *below*).

It is doubtful whether, in intact animals, any of the CORTICOIDS can produce a significant increase in muscular strength. Overdosage with desoxycorticosterone may cause profound asthenia in patients, and hypokalemic paralysis in dogs and monkeys (see below). Severe overdosage with corticoid hormones may even produce foci of muscular degeneration in experimental animals.

Nervous System and Sense Organs. — *Adrenalectomy* has no permanent direct effect upon the NERVOUS SYSTEM, although, perhaps partly through the resulting fatigue, depression and cachexia it diminishes the fighting instinct and libido of animals.

Adrenaline likewise fails to produce any clear-cut and specific direct effect upon peripheral nerves. It is *useful in local anesthesia because, due* to its local vasoconstrictor effect, it delays the absorption, and thus prolongs *the action* of admixed anesthetics (e.g., novocain). At the same time, it conveniently decreases bleeding. Certain *adrenaline derivatives* (e.g., benzedrine) are valuable central stimulants which temporarily combat mental fatigue, somewhat like caffein does Such stimulation is usually followed by a period of depression

Corticoids elicit general anesthesia, if given in a manner to cause a *rapid* and pronounced increase in the hormone concentration of the circulating blood. *In the event of* chronic desoxycorticosterone overdosage, a periodic type of muscular paralysis ensues This is accompanied by hypopotassemia and is curable by the administration of potassium. It bears a striking resemblance to the so-called "familial paralysis" of clinical pathology. The occasional convulsive seizures of *experimental animals*, chronically treated with desoxycorticosterone, are usually due to the development of *periarteritis nodosa* in the brain, a lesion which may even cause fatal cerebral apoplexy.

In the EYE, *adrenaline causes dilatation of the pupil, due to an excitation* of the dilator muscle of the iris. This is of practical value in ophthalmology since adrenaline mydriasis facilitates ophthalmoscopic examinations and the readiness with which it is obtained has diagnostic significance in certain diseases of the eye. The effect is particularly pronounced following denervation of the iris by excision of the superior cervical ganglion. The hormone also causes protrusion of the eyeball in certain animal species. This is due to contraction of Mueller's muscles and retraction of the upper eyelid. The *retraction of the nictitating membrane* (e.g., in the cat) by adrenaline is likewise greatly increased by sympathetic denervation. The hormone may elicit lachrymation. Its purported value in the treatment of glaucoma is far from being reliable.

The marked vasoconstrictor effect of adrenaline, especially when locally applied to the mucous membranes of the NOSE is of practical value in combatting the nasal hyperemia of hay fever and rhinitis.

Digestive System. — Adrenaline inhibits both the tone and the peristalsis of the smooth musculature in STOMACH *AND INTESTINES* This intestinal inhibition occurs in vitro even in concentrations of adrenaline as low as 1:400,-000,000, and because of this great sensitivity it has been used as a basis for the bioassay of the hormone (See: p 100.) On the other hand, the pyloric, ileocolic and internal-anal sphincters are stimulated by adrenaline.

male accessory sex organs, such as the seminal vesicles, prostate, epididymis, vas deferens and preputial glands of mammals, the comb of the capon, etc.

Various Other Effects. — REGENERATION AND WOUND HEALING are markedly impeded by adrenalectomy and restored towards normal by corticoids, but not by adrenaline.

The ESTRUS cycle is deranged and usually, permanent diestrus ensues following adrenalectomy in various animal species.

Adrenalectomy performed during PREGNANCY usually results in abortion, unless suitable corticoid therapy is instituted. Adrenaline is unable to maintain gestation under such conditions.

Adrenalectomy causes almost immediate cessation of milk secretion, if performed during the period of LACTATION. Cortical hormones (but not adrenaline) may restore milk secretion, under such conditions. It has not been proven, although it is claimed by some, that a special cortical hormone, "cortilactin" is responsible for the maintenance of lactation. (See also p. 115.)

HIBERNATION may be temporarily interrupted by adrenaline injection in certain animals, perhaps because of the metabolism-stimulating effect of the hormone.

ADRENAL HORMONE CONTENT OF BODY FLUIDS AND TISSUES

ADRENALINE

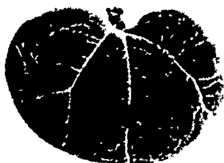
It is still a debated question whether adrenaline is continuously secreted by the medulla or whether it is discharged only during emergencies. Since any type of stress causes a discharge of adrenaline, it is difficult to estimate its NORMAL BLOOD CONCENTRATION, because the excitement, incident to the determination, in itself causes adrenaline secretion in experimental animals In any case, it is safe to conclude, that under resting conditions, the adrenaline concentration of the blood is so low (less than about 1 : 1,000,000,000), that it exerts no physiologic effects.

The emergency hyperadrenalinemia is due, firstly, to a discharge of hormone-saturated blood from the large venous sinuses of the medulla. The latter are evacuated during emergencies, owing to a relaxation of the venous sphincters. Secondly, the adrenaline granules stored in the chromaffin cells, are discharged and hence during stress the adrenaline content of the adrenal decreases parallel with the increase in blood adrenaline. This hyperadrenalinemia is characteristic of the first stage of the alarm reaction and accounts for many of the manifestations seen in this initial phase of a general-adaptation-syndrome (hyperglycemia, loss of hepatic glycogen, transitory rise in blood pressure, tachycardia).

The ADRENALINE CONTENT OF THE RESTING ADRENAL is about 0.1% of its wet weight and the total hormone content of the two glands amounts to about 10 mg. in man. It is well to remember that the normal adrenal medulla actually contains more than the fatal dose (about 2 mg intravenously or 8 mg. subcutaneously) of this hormone This is especially noteworthy in connection with adrenal surgery, since mere massage of the gland is likely to cause a dangerous sudden discharge of adrenaline into the circulation.

REMOVAL OF THE VARIOUS ENDOCRINE GLANDS has comparatively little effect upon the adrenaline content of the blood and the adrenal medulla. This is particularly noteworthy as regards hypophysectomy. This operation causes a marked decline in the function of the adrenal cortex, but apparently remains without significant effect





Nephrosclerosis produced by desoxycorticosterone in the cat. Compare granular surface of nephrosclerotic kidney of desoxycorticosterone-treated cat (top) with smooth surface of normal control kidney The treated animal received 20 mg/day of desoxycorticosterone during six weeks and was sensitized by a high sodium diet

CORTICOIDS (especially desoxycorticosterone) augment diuresis, probably *through the inhibition of the tubular* reabsorption of filtrate. Following chronic overdosage with desoxycorticosterone, marked glomerular lesions occur. These are similar to those of malignant nephrosclerosis in clinical medicine. There is hyalinization, *especially of the afferent glomerular* arterioles, and eventually complete hyalinization of the entire glomerular tuft. Increased permeability of the glomerular vessels to protein results and this leads to *the formation of* numerous hyaline casts, which occlude the lumina of the nephron and cause cystic dilatation of the segments proximad to the casts. These changes are often accompanied by hypertension, pyelonephritis, nephritis and marked edema of the connective tissue surrounding the renal pelvis. Diets rich in Na aggravate these lesions, while a *high intake of acidifying salts,* carbohydrates and vitamins tend to prevent them.

Accessory Sex Organs. — ADRENALECTOMY causes some involution of the accessory genital organs in both sexes. Presumably this is partly due to lack of cortical steroid sex hormones, but it is difficult to estimate *the extent to which it is merely the* result of non-specific damage and the subsequent gonadal atrophy.

One of the most characteristic effects of ADRENALINE is the contraction of the pregnant or non-pregnant uterus in most animal species. In the cat, rat, *mouse, guinea pig and man,* the uterus is contracted by adrenaline only during pregnancy, while in the non-pregnant animal the hormone actually causes inhibition of the uterus. Thus, *its actions differ from those of oxytocin.* (See · Hypophysis.)

CORTICOIDS (e.g., desoxycorticosterone) possess both folliculoid and luteoid activities, the latter being, by far, more prominent. *Thus, in the* castrate female, suitably pretreated with folliculoids, the administration of desoxycorticosterone induces progestational proliferation of the endometrium and even renders deciduoma formation possible.

None of the life-maintaining corticoids have yet been shown to exert any typical testoid effects. On the other hand, it will be kept in mind that pure testoids (e.g., dehydro-iso-an*drosterone, androsterone, adrenoster*one) are also produced by the cells of the adrenal cortex. These latter compounds stimulate the growth of

of the adrenal itself. According to one author, the average output of one suprarenal gland/minute/Kg. body weight, is equivalent to the activity that can be extracted from 0 6 gm. of ADRENAL TISSUE. Under certain conditions of stress, the corticoid activity of 1 cc. of suprarenal plasma may be 10 times as high as that extractable from 1 gm. of gland.

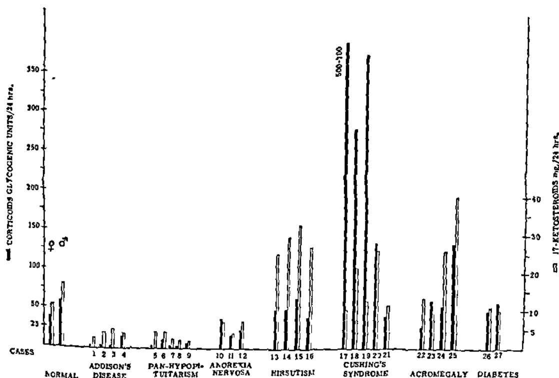
Noteworthy quantities of corticoid activity can also be extracted from the CORPUS LUTEUM, presumably because progesterone possesses corticoid potency. Other tissues have not been shown to possess any noteworthy degree of such activity.

Normal human URINE contains just detectable quantities of corticoid material.

HYPOPHYSECTOMY causes a pronounced diminution of the corticoid hormone content of the adrenals and SIMMONDS' disease diminishes, while CUSHING'S DISEASE increases the output of active corticoids through the urine. These observations are readily understandable if we remember that the function of the adrenal cortex is almost entirely under the control of hypophyseal corticotrophin. Active ADRENAL-CORTICAL TUMORS likewise raise the urinary corticoid titer. (For additional data see sections : The Steroids, Hypercorticoidism, Cushing's Disease, etc.)

Adrenal denervation, or stimulation of the adrenal NERVES, causes no change in corticoid hormone production. This indicates, that unlike the medulla, the cortex is not markedly influenced by nervous stimuli.

Urinary elimination of corticoids rises significantly in patients a few



Excretion of gluco-corticoids and of 17-KS in various endocrine and other disorders
(Courtesy of Drs E -H Venning and J -S L Browne)

upon the hormone production of the medulla.

Similarly, TREATMENT WITH VARIOUS HORMONE PREPARATIONS exerts comparatively little effect upon the adrenaline content of the adrenals and the blood. Insulin represents a notable exception, since the hypoglycemia which it elicits causes a compensatory increase in the production of adrenaline. Oral administration of adrenaline itself results in the urinary elimination of inactive adrenaline sulfate but otherwise the hormone is not excreted by the kidney in appreciable quantities.

Unlike the function of most other endocrine glands, that of the adrenal medulla is primarily under NERVOUS control. Indeed, most stimuli, affecting the adrenaline production of the medulla, become inactive after denervation of the gland. Conversely, stimulation of the great splanchnics causes an immediate and pronounced adrenaline discharge, and a special center for adrenaline secretion appears to exist in the upper part of the floor of the fourth ventricle. It is through the intermediary of the preganglionic splanchnic nerves that impulses, originating from this center, reach the adrenal medulla, whose cells are excited by the liberation of acetylcholine at the nerve endings. It has been shown that injected acetylcholine stimulates adrenaline secretion, both in the intact and in the splanchnicotomized animal and that splanchnic stimulation elicits acetylcholine production in the medulla. Thus the nervous stimulus of splanchnic excitation is transmitted to the medullary cells through the same humoral (acetylcholine) mechanism by which preganglionic sympathetic fibers act upon peripheral ganglion cells. Indeed, even on embryologic grounds, the chromaffin elements may be regarded as modified peripheral sympathetic ganglia. (See p. 115.)

It is probable that there are higher centers of adrenaline secretion, even above that of the fourth ventricle. Stimulation of the hypothalamus and even emotional stimuli, originating in the cerebral cortex, can cause adrenaline secretion. It will be recalled that emotional hyperglycemia and tachycardia are mainly due to adrenaline discharge. Only to a small extent are these phenomena mediated by excitatory sympathin liberated at nerve endings. In experimental animals, the slight residual adrenergic manifestation which persists after ablation of the adrenal medulla, can be completely eliminated by denervation of the liver, the main source of excitatory sympathin.

An immediate loss of adrenaline from the chromaffin cells and a parallel rise in blood adrenaline is also induced within a few seconds by MUSCULAR EXERTION, COLD, VARIOUS ANESTHETICS, SURGICAL TRAUMA, HEMORRHAGE, BURNS, INTOXICATIONS, etc. It is most probable, however, that all these agents act merely by eliciting an ALARM REACTION, since none of them have been proven to act directly upon the medullary cells. During such emergencies, as following splanchnic stimulation, the adrenaline output of the medulla may rise, from a negligible amount, to as much as 0.004 mg./Kg. body weight/minute. But all these non-specific damaging agents fail to cause adrenaline liberation, following denervation of the gland.

CORTICOIDS

No accurate data are as yet available concerning the corticoid hormone content of the BLOOD and TISSUES, but bioassays indicate that normally the corticoid potency of peripheral blood is negligibly small On the other hand, very large quantities of corticoids can be demonstrated in the venous blood

reticularis, here designated as the "X-zone," is especially prominent and dark in adult females, but absent in males. Spaying (ovariectomy) has no effect, but castration (testis extirpation) causes the appearance of the X-zone in males, which normally do not possess it. The X-zone may be the source of adrenal testoids and the presence of a functional testis may cause its compensatory involution. The development of this zone in castrates could then be viewed as a compensatory effort to maintain some testoid hormone production. This view — though not proven — receives further support from the observation that administration of purified testoids (e.g., testosterone) causes the disappearance of the X-zone in castrate males, presumably owing to a phenomenon of compensatory involution.

In some animal species adrenal-cortical cancers develop following gonadectomy (e.g., mouse, guinea pig).

REMOVAL OF OTHER ENDOCRINE GLANDS exerts no important effect upon adrenal structure, outside of that which could be explained on the basis of the general-adaptation-syndrome elicited by such operations.

Hormones. — The ADRENOTROPHIC effect of pituitary extracts appears to be due entirely to the adrenotrophic hormone (or hormones) of the anterior lobe cells. Only extracts of the anterior lobe cause adrenal-cortical enlargement and hyperfunction, while those of the middle and posterior lobe have no such effect.

ADRENALINE causes no very striking compensatory atrophy of the adrenal medulla but, as mentioned above, both gluco- and mineralo-CORTICOIDS produce marked compensatory involution of the adrenal-cortical cells.

INSULIN causes degranulation of the chromaffin cells, since the hypoglycemia which it produces calls forth a compensatory secretion of adrenaline, to normalize the blood sugar level.

FOLLICULOIDS elicit a pronounced and rather specific type of cortical hypertrophy, much greater than could be accounted for by their non-specific damaging action.

TESTOIDS tend to decrease the size of the adrenal cortex, in all species so far examined. As previously stated, in certain strains of mice, the testoids prove particularly potent in causing the disappearance of the "X-zone" in females and castrate males, in which it is normally prominent. In other species (e.g., rat) testoids cause a peculiar type of vacuolization and atrophy of the adrenal cortex.

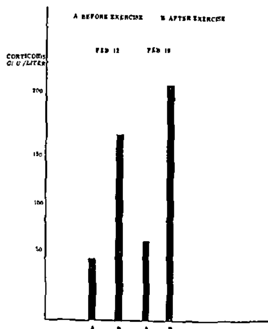
OTHER ENDOCRINE PREPARATIONS do not appear to have a very specific effect upon the adrenal, but tend to cause hypertrophy of the cortex in proportion to other manifestations of the general-adaptation-syndrome, which they elicit. It is not surprising, therefore, that heavy overdosage with *thyroxin*, which induces serious metabolic disturbances, is particularly effective in causing cortical hypertrophy.

None of these hormone preparations (with the possible exception of folliculoids), are effective in hypophysectomized animals and hence it is generally agreed that their effect is mediated by the anterior-hypophysis.

Diseases. — As may be expected, HYPOPITUITARISM causes involution, while HYPERPITUITARISM usually induces hyperplasia and hypertrophy of the adrenal cortex.

The adrenal lesions associated with various clinical forms of HYPO- and HYPERADRENALISM are discussed in the sections devoted to the latter.

In certain very acute INFECTIONS the adrenal stimulation is so pronounced that hemorrhages and necroses ensue in the suprarenals, with a secondary breakdown of their function. — *Waterhouse-Friedrichsen's syndrome*, usually elicited by acute meningococcic septicemia, is a typical case in point.



Effect of strenuous exercise on the excretion of corticoids in a group of 14 army recruits. (After E.-H. Venning and V. Kazmin Endocrinology 39, 131, 1946.)

hours after traumatic injuries, acute muscular exertion, burns, acute infections, etc., all of these, are conditions capable of eliciting an ALARM REACTION. The bulk of the corticoids produced are probably eliminated in the urine, after *transformation into inactive metabolites*. Hence, bioassays *for the corticoid activity of urine can* give, at best, only an approximation of *the total quantity of cortical steroid* production.

From the above data it appears that both adrenaline and corticoids are *produced in large quantities under the* influence of essentially the same types *of non-specific damaging agents, the* former somewhat more rapidly than *the latter.*

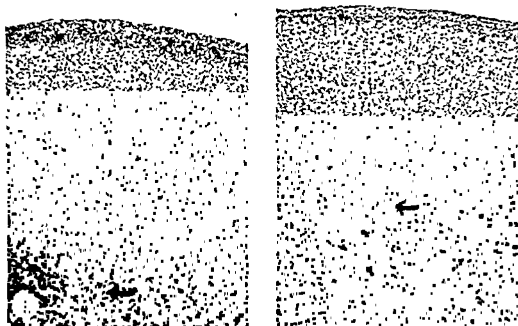
STIMULI INFLUENCING ADRENAL STRUCTURE

Extirpation of Endocrine Glands. — PARTIAL ADRENALECTOMY induces marked compensatory hypertrophy of the remaining cortical cells, without any comparable enlargement of the *residual medullary elements.* This is perhaps due to the fact that only cortical cells are capable of producing significant amounts of corticoids, while sympathetic nerve endings and paraganglia may substitute to some extent for the partial loss of chromaffin cells, *even without compensatory proliferation* of the medullary remnant. — It is well to remember that very minute cortical islets suffice to maintain adrenalectomized animals alive, and the compensatory hypertrophy of hardly visible cortical cell islets, or ectopic adrenal cortices, may explain the survival of supposedly completely adrenalectomized animals. The same applies to patients having destructive cortical lesions.

Treatment *with large doses of gluco-* or mineralo-corticoid hormones prevents compensatory hypertrophy after partial adrenalectomy.

HYPOPHYSECTOMY causes atrophy of the adrenal cortex, but does not influence the structure of the medulla *significantly. In hypophysectomized* animals, compensatory hypertrophy of cortical remnants does not occur after partial ablation of the gland, nor is there any cortical enlargement during the general-adaptation-syndrome. On the other hand, adrenocorticotrophic *extracts of the anterior-pituitary* stimulate the adrenal cortex, even in the hypophysectomized animal It has been assumed therefore that the phenomena of "compensatory" and "damage hypertrophy" *of the adrenal cortex are due* to increased secretion of adrenocorticotrophic hormones, by the anterior lobe cells of partially adrenalectomized or damaged animals

Important changes in the adrenal cortex of certain species, especially certain strains of mice, are induced by GONADECTOMY In these strains the zona



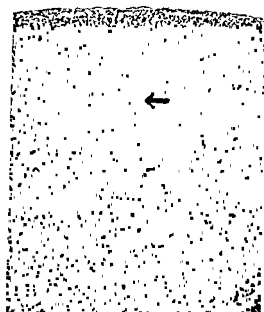
Effect of hypophysectomy and of various steroid hormones upon adrenal cortex. — A. Adrenal of a normal 3-month- [illegible] zones In this and [illegible] weight 44 mg). — [illegible] atrophy of the cortex, which affects all layers, but especially [illegible] The medulla remains normal (adrenal weight 15 mg) — C. Adrenal of similar rat receiving increasing doses (0 5 to 3 mg /day) of desoxycorticosterone acetate during 3 months. Note pronounced involution of cortex, while medullary cells remain normal (adrenal weight 23 mg). — D. Adrenal of similar rate treated with estradiol (100 γ/day during 9 months). Note enlargement of entire cortex which takes up the whole visual field There is marked hyperemia with great dilatation of cortical sinusoids. The glomerulosa, however, is inconspicuous (adrenal weight 122 mg). — E. Adrenal of similar rat treated with small doses of testosterone (implantation of one 14 mg pellet of methyl-testosterone one month prior to autopsy) Note extreme density of glomerulosa zone (adrenal weight 30 mg). — F. Adrenal of similar rat receiving large doses of a testoid (10 mg of methyl-testosterone/day during 3 months) Note density of glomerulosa and atrophy of cortex. The latter is studded with vacuolated signet-ring cells ' which are very characteristic of rats chronically overdosed with large amounts of testoids (adrenal weight 28 mg)

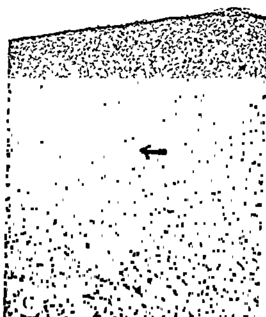
OTHER DISEASES rarely cause any striking or specific changes in the adrenals, except the cortical hyperplasia and hypertrophy, which are almost constant accompaniments of any disease. (See . General-Adaptation-Syndrome.)

Diet. — Undernutrition, and especially deficiency in ascorbic acid or the vitamin-B complex, cause pronounced enlargement of the adrenal cortex. Diets rich in protein are most, and diets high in carbohydrates least favorable for the development of cortical enlargement, during the general-adaptation-syndrome.

The ascorbic acid and cholesterol content of the adrenal cortex, partly depend upon the dietary intake of ascorbic acid and cholesterol respective-






C


D

ly. It is noteworthy that in the guinea pig, which is particularly sensitive to ascorbic acid deficiency, this avitaminosis elicits not only an almost complete loss of adrenal ascorbic acid but also severe degenerative and hemorrhagic lesions in the suprarenals.

Nervous Stimuli. — Denervation of the adrenals, or even mere transection of the splanchnic nerves, prevents the loss of chromaffin granules, otherwise occurring in the alarm reaction elicited by diverse non-specific agents. On the other hand, injection of acetylcholine, causes loss of chromaffinity, even following denervation, since this substance is the direct humoral transmitter of secretory stimuli to the adrenal medulla.

The appearance of the adrenal cortex, and its response to hormonal or noxious stimuli, remain practically unaltered by denervation of the gland. Stimulation of the adrenal nerves also fails to elicit any characteristic morphologic change in the cortex

Age. — Soon after birth, the human adrenal cortex undergoes a process of so-called *"physiologic degeneration"* This is characterized by a great decrease in cortical width and the appearance of deep convolutions on the surface of the gland. The process begins during the first days after birth and is usually terminated by the end of the first to third month In three-month-old babies, the adrenals weigh only about half as much as in the newborn.

Sex. — In general, the adrenals of female animals are considerably larger than those of males. The sexual dimorphism of the mouse adrenal (the so-called "X-zone") has been mentioned in connection with the results of gonadectomy. (See p 130.)

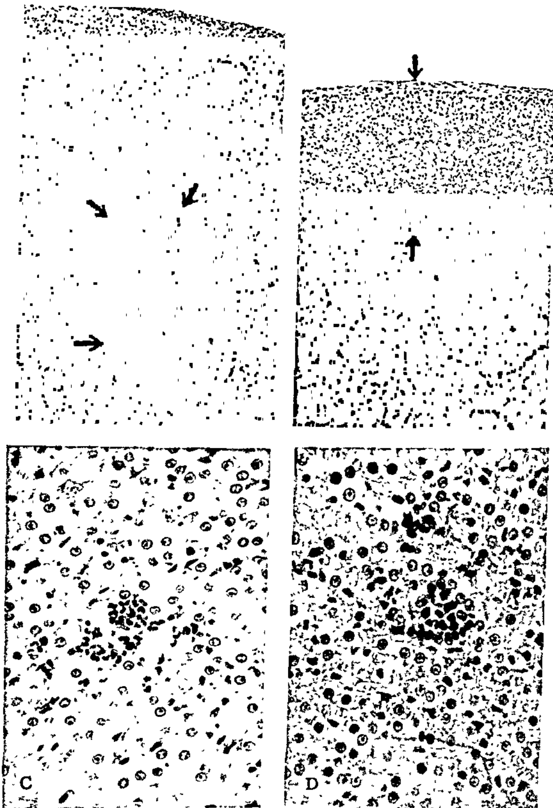
Estrus, Pregnancy and Lactation. — Estrus, pregnancy and lactation exert no significant influence upon the *adrenal medulla, but the cortex is somewhat enlarged during all these conditions.*

Seasonal Changes and Hibernation. — In hibernating animals, both the cortex and the medulla undergo atrophy and there may be almost complete loss of chromaffinity in the medullary cells, during the winter season

Other Conditions. — ANAPHYLAXIS, REDUCED ATMOSPHERIC PRESSURE, EXTREME HEAT OR COLD, SEVERE MUSCULAR WORK, HEMORRHAGE, BURNS, TRAUMATIC SHOCK AND A LARGE VARIETY OF DRUGS cause loss of chromaffinity from the adrenal medulla, loss of lipid and ascorbic acid granules with hypertrophy and hyperplasia of the adrenal cortical cells, that is, histologic signs of increased adrenaline and corticoid hormone secretion All these phenomena run closely parallel with the general damaging effects of these agents and must be regarded as part of the general-adaptation-syndrome which they elicit. Their effect on the medulla is mediated by the sympathetic and prevented by adrenal denervation or splanchnicotomy; their influence upon the cortex is mediated by the anterior lobe and prevented by hypophysectomy

sodium diet. Note gre[illegible]
necrosis of the cortex
weight 283 mg). — [illegible]
adrenals almost com[illegible]
These pictures show that anterior-pituitary extracts can not only stimulate the adrenal cortex, but, in the event of overstimulation (perhaps by producing adrenal periarteritis nodosa) cause [illegible]

posing protein material



Effect of anterior-lobe extracts upon the adrenals. — A. Adrenal of an adult male rat receiving 20 mg of lyophilized anterior-pituitary tissue daily during 30 days The animal was sensitized to the corticotrophic action of the extract by castration, unilateral nephrectomy and a high-

Extra-adrenal chromaffin tissue is so widely distributed in the normal organism that it would be difficult to identify ACCESSORY ADRENAL MEDULLAE, *even if they did occur.*

TRUE ACCESSORY ADRENALS, containing both cortical and medullary tissue, are extremely rare. They may be formed by the early embryonic separation of a portion from the main adrenal primordium or through the invasion of separate nodules of interrenal cortical tissue by adjacent sympathogonia.

Among OTHER MALFORMATIONS of the adrenals, only the very rare "butterfly adrenal" is worth mentioning. It results from the development of a connecting bridge between the two adrenals

The diagnosis of adrenal malformations is hardly ever possible in the living patient, unless they are accidentally noted on the occasion of a laparotomy.

Clinical manifestations are rare, but if they occur, they are identical with hypo- or hyperadrenalism due to other causes and must be treated in the same manner. (See : Hypocorticoidism, Hypercorticoidism.)

VASCULAR DISTURBANCES

HEMORRHAGES into the adrenal parenchyma are frequently observed in new-born infants, especially in premature babies. They are rarely sufficiently extensive, however, to cause severe insufficiency symptoms.

Small patches of necrosis and hemorrhage are common in the adrenals of experimental animals and man exposed to various types of acute non-specific damage, conducive to an alarm reaction (e.g., Waterhouse-Friedrichsen syndrome).

THROMBOSES of the adrenal veins sometimes occur in acute infections and intoxications. They may be bilateral and conducive to "apoplexy of the adrenals," with symptoms of acute fatal insufficiency.

DEGENERATIONS

CALCIFICATION of the adrenals, sometimes accompanied by OSSIFICATION, *may occur as sequelæ* of local tuberculosis, degeneration and tissue necrosis.

AMYLOID degeneration of the adrenals is rarely pronounced except as part of generalized amyloidosis. It is sometimes associated with adrenal (and renal) vein thrombosis, but seldom with hypocorticoidism.

INFLAMMATIONS

ACUTE INFLAMMATION of the adrenals is rare, although, in generalized septicemia, foci of infection may become localized in one or both suprarenal glands.



Calcification and ossification of the adrenal. Note calcium deposit (dark) and beginning bone formation (light) among adrenal-cortical cell columns

The so-called "PRIMARY CONTRACTED ADRENAL" is probably a special type of chronic inflammation, characterized by round cell infiltration and connective tissue stroma proliferation. It causes gradual destruction of the gland with addisonian symptoms.

Rays. — The adrenal glands (both normal and neoplastic) are comparatively resistant to the damaging effect of X-RAYS and, it has even been claimed that in small doses, X-ray treatment may stimulate the function of adrenal cells. Heavy overdosage with *X-rays* causes degenerative changes, and even necrosis, both in the cortex and in the medulla.

DISEASES OF THE ADRENALS

MALFORMATIONS

It is doubtful whether complete APLASIA of the adrenals ever occurs. Supposedly pertinent cases have been reported in the literature but in these the possibility of a secondary destruction of the adrenals, during postnatal *or even fetal life, must always be con*sidered. It will also be kept in mind that complete aplasia of the adrenals is incompatible with the maintenance of postnatal life and could, therefore, never be observed in an adult.

Isolated aplasia of the adrenal medulla would theoretically be compatible with the maintenance of life, but allegedly relevant instances are also more probably *due to secondary destruction* by disease.

As with several other endocrine glands, we have no means of identifying a primary HYPOPLASIA of the adrenal cortex. The postnatal condition of the cortex is so largely under pituitary con*trol, that any instance of insufficient* development raises the suspicion of a secondary atrophy, due to anterior pituitary failure, from which it could not be distinguished on morphologic grounds. The literature contains descriptions of so-called cortical hypo*plasia in new-born infants with anencephaly, hydrocephalus* and other malformations of the brain, but here a concomitant primary failure in the development of the anterior lobe appears to give the most satisfactory explanation of the deficient adrenal-cortical development.

Similarly, cases of so-called cortical aplasia in one gland of a patient with a *contralateral cortical tumor,* are usually due *to compensatory cortical atrophy,* rather than true malformation.

In *status thymico-lymphaticus,* hypoplasia of both cortex and medulla have repeatedly been described, without there being any definite proof that the subnormal suprarenals are malformed, *rather than involuted.*

As far as we know, HYPERPLASIA of the adrenal cortex is always due to excess adrenotrophin secretion. It almost invariably gives rise to clinical manifestations of corticoid hormone overproduction and will be discussed in the corresponding section *on hyper*corticoidism.

Diffuse primary hyperplasia of the medulla has never been proven to occur, although adenomas and other tumors of the chromaffin cells are comparatively common.

ACCESSORY ADRENAL CORTICES are the most common malformations of the gland both in animals and in man. Their *chief importance lies in the fact* that they prevent the appearance of deficiency symptoms after complete destruction or surgical removal of the main glands. They are particularly common in some strains of rabbits, mice and rats, but much less frequent in the cat, dog, monkey and guinea pig. In man, accessory cortices tend to occur in the vicinity of the spermatic arteries, the testis and epididymis, the ovaries and their ligaments, *the hepato-duodenal* ligament, the mesentery and the kidney. Apparently, many accessory cortices disappear during postnatal life, since such structures are much more common in the testis region of boys, than in adults.

Extra-adrenal chromaffin tissue is so widely distributed in the normal organism that it would be difficult to identify ACCESSORY ADRENAL MEDULLAE, even if they did occur.

TRUE ACCESSORY ADRENALS, containing both cortical and medullary tissue, are extremely rare. They may be formed by the early embryonic separation of a portion from the main adrenal primordium or through the invasion of separate nodules of interrenal cortical tissue by adjacent sympathogonia.

Among OTHER MALFORMATIONS of the adrenals, only the very rare "butterfly adrenal" is worth mentioning. It results from the development of a connecting bridge between the two adrenals.

The diagnosis of adrenal malformations is hardly ever possible in the living patient, unless they are accidentally noted on the occasion of a laparotomy.

Clinical manifestations are rare, but if they occur, they are identical with hypo- or hyperadrenalism due to other causes and must be treated in the same manner. (See . Hypocorticoidism, Hypercorticoidism.)

VASCULAR DISTURBANCES

HEMORRHAGES into the adrenal parenchyma are frequently observed in new-born infants, especially in premature babies. They are rarely sufficiently extensive, however, to cause severe insufficiency symptoms

Small patches of necrosis and hemorrhage are common in the adrenals of experimental animals and man exposed to various types of acute non-specific damage, conducive to an alarm reaction (e g . Waterhouse-Friedrichsen syndrome)

THROMBOSES of the adrenal veins sometimes occur in acute infections and intoxications. They may be bilateral and conducive to "apoplexy of the adrenals," with symptoms of acute fatal insufficiency.

DEGENERATIONS

CALCIFICATION of the adrenals, sometimes accompanied by OSSIFICATION, may occur as sequelæ of local tuberculosis, degeneration and tissue necrosis.

AMYLOID degeneration of the adrenals is rarely pronounced except as part of generalized amyloidosis. It is sometimes associated with adrenal (and renal) vein thrombosis, but seldom with hypocorticoidism.

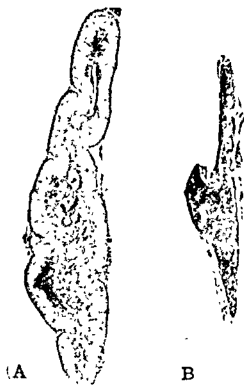
INFLAMMATIONS

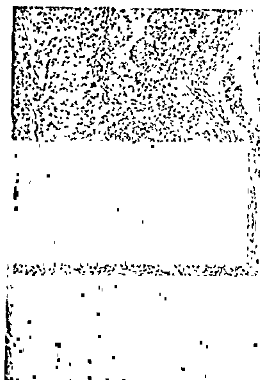
ACUTE INFLAMMATION of the adrenals is rare, although, in generalized septicemia, foci of infection may become localized in one or both suprarenal glands



Calcification and ossification of the adrenal. Note calcium deposit (dark) and beginning bone formation (light) among adrenal-cortical cell columns

The so-called "PRIMARY CONTRACTED ADRENAL" is probably a special type of chronic inflammation, characterized by round cell infiltration and connective tissue stroma proliferation. It causes gradual destruction of the gland with addisonian symptoms





Primary contracted adrenal in Addison's Disease. (Courtesy of Dr. T. Waugh) — A. Cross-section through normal human adrenal (low magn) — B. Cross-section through primary contracted adrenal in Addison's disease (same magn as A) — C. Higher magnification of adrenal shown in fig B Note almost complete replacement of cortex and medulla by connective tissue and lymphocytes



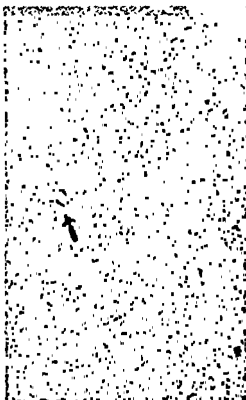
Amyloidosis of the adrenals Hormogeneous amyloid deposits in adrenal cortex Endocrine cells are compressed and atrophic



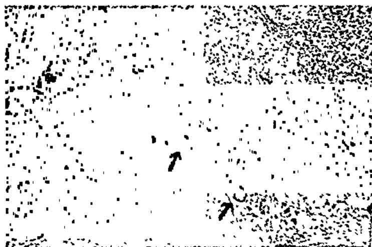
Primary contracted adrenal. (Courtesy of Dr W Boyd) Note that adrenal parenchyme is almost completely replaced by connective tissue and lymphocytic infiltration The patient suffered from Addison s disease



Primary contracted adrenal. So-called "primary contracted adrenal" with cortical atrophy in a patient who died from Addison's disease. Note intense lymphocytic infiltration especially around the large vein (top) while remaining cortical cells (bottom) are enlarged, due to compensatory hypertrophy. Small dots between cortical cells are erythrocytes, due to bleeding into hyperactive, hyperemic cortical remnant.



Tuberculosis of the adrenals. Caseous tuber-



Adrenal tuberculosis. Note polynuclear giant cells (arrows), lymphocytic infiltration, epithelioid cells and caseation. The remaining cortical cells (top) appear to be enlarged, perhaps due to compensatory hypertrophy. The patient suffered from Addison's disease.

The most common inflammatory lesion in the adrenal is TUBERCULOSIS, which is frequently bilateral and conducive to Addison's disease. It may, or may not, be accompanied by widespread tuberculous lesions in other organs, and is, of course, always of hematogenous origin. It is not known why tuberculosis has such a predilection for localization in the suprarenals.

SYPHILIS likewise exhibits a special affinity for the adrenals. *Congenital syphilis*, tends to produce miliary necroses. Spirochaetes are very regularly present, in the adrenals of syphilitic new-born, even if anatomic lesions are not observed.

Acquired syphilis may lead to diffuse gumma formation or to more or less generalized sclerosis of the adrenals, either of which may be the cause of Addison's disease. In certain cases, antisyphilitic therapy has markedly improved the condition of addisonians whose endocrine deficiency was due to adrenal syphilis. It is also noteworthy that tertiary syphilis quite frequently causes amyloid degeneration of the adrenals.

HYPOCORTICOIDISM (ADDISON'S DISEASE)

(SYNONYMS: Morbus Addisonii, adreno-cortical deficiency, hypoadrenalism, hypoadrenia, adrenal deficiency.)

DEFINITION

Addison's disease is a condition in which the hormone production of the adrenal cortex is sufficiently diminished to cause detectable deficiency manifestations. Although Addison described only one type of this disease, it is customary to use the term "Addison's disease" as synonymous with hypocorticoidism.

The condition is often designated simply as "adrenal deficiency," since hypofunction of the medulla hardly ever produces any manifestations of insufficiency, yet the term "hypocorticoidism" is more precise.

CLASSIFICATION

The clinical types of Addison's disease may be classified according to various points of view.

According to the MAIN MANIFESTATIONS, we may distinguish:

(A) ACUTE FORMS

(1) *The sudden, unexpected death of adrenal failure* usually appears without any warning, in patients in whom there was never any cause to suspect adrenal insufficiency. Death may occur with epileptiform or angina pectoris-like symptoms. A slight trauma, childbirth, exhaustion or some other, often quite trivial, damage may be fatal. At autopsy, one finds almost complete destruction of the adrenals by disease or mere "adrenal hypoplasia." Most of these cases are closely related to the so-called "status thymico-lymphaticus."

(2) The *pseudoperitonitic form* is the most common acute type. In its symptomatology, it resembles acute appendicitis, peritonitis or the rupture of an ectopic pregnancy. There is intense abdominal pain, meteorism, facies peritonitica, vomiting, hiccup and a very rapid and weak pulse. Death ensues a few days, or even hours, after the onset of the symptoms. In such cases, autopsy often reveals complete destruction of the adrenals due to thrombosis or massive hemorrhage

(3) The *choleriform or gastrointestinal type* resembles acute food poisoning or gastrointestinal septicemia There is vomiting, persistent diarrhea, cold sweats, anuria, hypothermia and death ensues within a short time.

(4) The *apoplectiform type* simulates a stroke. The patient suddenly collapses and enters a deep coma, which

is but occasionally interrupted by convulsive spells or deliria. This form is also rapidly fatal and often due to massive bilateral adrenal hemorrhage.

(5) The *meningo-encephalitic form* imitates acute encephalitis or meningitis, particularly tuberculous meningitis, because the sugar in the spinal fluid may be low in either case.

(6) The *myocardial form*, described by the French school as "asystolie surrénale," in which a fall in blood pressure and cardiac failure, often combined with arrhythmia, lead to death from cardiovascular failure, without any prominent anatomic change in the myocardium.

These acute forms are much less common than the chronic types of Addison's disease and there is usually considerable overlapping between the various types.

(B) Chronic Forms

(1) *Typical chronic Addison's disease* is by far the most common type Its main symptoms are: asthenia with dizziness and syncopal attacks, hypotension with decrease in blood volume and circulatory failure, loss of weight, pigmentation of the skin and mucous membranes, gastrointestinal disturbances with anorexia, nausea, diarrhea, hiccups and vomiting, a tendency towards hypoglycemia and great sensitivity to various types of strain (e g , cold, muscular fatigue, intoxications and infections).

(2) The *chronic, nervous or solar type*, in which crises of solar neuralgia, with nausea and vomiting, alternate with periods of severe psychic disturbances, such as melancholia or spells of acute delirium with maniacal excitement. Occasionally, epileptiform convulsions are associated with a solar crisis. All these nervous disturbances are combined with typical signs of adrenal insufficiency, such as asthenia, pigmentation of the skin and mucous membranes.

In these chronic cases, the eliciting cause is about as frequently caseous adrenal tuberculosis as "primary contracted adrenal." Other etiologic lesions are rare.

According to the INTENSITY of the insufficiency syndrome, it is customary to recognize:

(1) *Mild cases* (also known as constitutional addisonism, temporary addisonism or "formes frustes"), which are generally due to a merely functional disturbance It is debatable whether these should be included in the concept of Addison's disease.

(2) *Severe Addison's disease* which is the common result of extensive cortical destruction

Obviously, it is also possible to classify pertinent cases according to their ETIOLOGY, thus distinguishing syphilitic, tuberculous, carcinomatous, etc., types of hypocorticoidism, since the various classifications overlap.

PATHOLOGIC ANATOMY

Addison's disease may be produced by a variety of adrenal lesions:

(1) "The PRIMARY CONTRACTED ADRENAL," as mentioned above, is the result of chronic inflammatory and degenerative lesions of unknown etiology. Usually both suprarenals are affected and after a period of connective tissue stroma proliferation and round cell infiltration, cortical atrophy ensues, due to extensive sclerosis of the parenchyme. It is often seen as a result of chronic intoxications and infections and may be related to the so-called "stage of exhaustion" of the general-adaptation-syndrome

(2) TUBERCULOSIS of the adrenals used to be the most common anatomic change seen in patients with Addison's disease, but in recent years, adrenal atrophy is increasingly more often encountered In the case of tuberculosis, the parenchyma is more or less completely destroyed by the granuloma and the caseous necrosis. It must be kept

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ism due to primary pituitary failure is more common in women, who are generally more susceptible to hypophyseal disease. In large statistical series, in which the various types are considered conjointly, males usually predominate over females in the ratio of 2 to 1.

Temporary addisonism is frequently seen in the course of PREGNANCY, apparently because the corticoid hormone requirements rise during gestation. This also explains why, if an addisonian woman becomes pregnant (which is rarely the case), her condition tends to become more severe and artificial interruption of gestation may become necessary. The rare cases, in which an improvement was noted during the late stages of gestation, are explained by assuming that the fetal cortex gradually begins to compensate for the insufficiency of the mother's adrenal.

It has been claimed that RACIAL FACTORS are of importance and that Addison's disease is most common in highly pigmented southern populations (e.g., Spaniards), but this has not been confirmed; the malady is not infrequent among blond Scandinavians. On the other hand, it has also been stated, that the disease is rare in the negro, yet many authentic cases have been described as occurring in colored people It is probable that Addison's disease is often not recognized in the negro patient because the most striking symptom, the pigmentation, is difficult to judge. Conversely, in the less markedly pigmented southern Europeans, the comparative darkness of the skin awakens a suspicion of Addison's disease, whenever the patient becomes debilitated from unknown causes Definite proof of an important hereditary factor, in the pathogenesis of Addison's disease, is lacking

PATHOGENESIS

Classical Addison's disease is due to a PRIMARY destruction of the adrenal cortex, by a local, directly acting, pathogenic agent ("primary contracted adrenal," tuberculosis, syphilis, carcinoma, hemorrhage, etc.), within the suprarenal gland itself. Hypocorticoidism may, however, also be caused by SECONDARY adrenal-cortical involution, due to anterior-pituitary failure and perhaps even by excessive stimulation of the adrenals through adrenotrophic hormones, which eventually lead to exhaustion atrophy of the cortical cells The most common causes of relative (in proportion to the requirements) or "functional" hypocorticoidism are cachexia, regional ileitis, ulcerative colitis, sprue and malaria.

The morphology of the adrenal changes, occurring in Addison's disease, have been discussed in the chapter on Pathologic Anatomy. The pathogenesis of the individual manifestations of adrenal-cortical insufficiency will be considered in the next chapter, entitled "Clinical Course," where these manifestations are described.

CLINICAL COURSE

State. — In typical cases, the course of Addison's disease is very characteristic There is, firstly, an extraordinary debility and languor, usually following upon some infection of the upper respiratory tract; secondly, the full syndrome of chronic Addison's disease (see below) and thirdly, decrease in blood volume and fatal circulatory collapse ensue during a crisis.

The leading symptoms and signs of the fully developed syndrome are :

(1) Gastrointestinal disturbances with loss of appetite, nausea with vomiting (almost a "sine qua non" in the diagnosis).

(2) Loss of weight.

(3) A typical brownish pigmentation of the skin and mucous membranes.

(4) Marked muscular weakness with easy fatigability

(5) Arterial hypotension with spells of dizziness

in mind that usually, *compensatory cortical* hypertrophy, hyperplasia and adenoma formation tend to proceed simultaneously with the adrenal destruction Hence, manifestations of hypocorticoidism remain latent until the regenerative power of the cortex is exhausted or a final hemorrhage destroys the residue of *functional cortical* tissue.

(3) SYPHILIS of the adrenals tends to produce Addison's disease only if widespread lesions, usually gummas, destroy most of the cortical parenchyme. This form is now comparatively rare, since tertiary syphilis has become less *frequent, due to the advances* in antisyphilitic therapy.

(4) Bilateral, non-functional, primary or, more often, secondary adrenal TUMORS cause Addison's disease, if they destroy the major part of the cortical tissue.

(5) THROMBOSIS of the adrenal blood vessels produces rapid destruction of the gland, which usually leads to the most acute types of Addison's disease

(6) Adrenal AMYLOIDOSIS is rarely the cause of hypocorticoidism.

(7) TRAUMATIC INJURIES of the adrenal region are also very exceptional causes of hormonal insufficiency.

(8) POLYGLANDULAR INSUFFICIENCY may affect the adrenal cortex and cause *functional failure, but it is very probable* that most of the allegedly relevant cases, actually represent PITUITARY INSUFFICIENCY *syndromes. It is noteworthy* that, even severe pituitary failure rarely elicits the typical syndrome of Addison's disease with gastrointestinal crises, hyperpigmentation, etc., although a few pertinent cases have been authenticated by autopsy Perhaps the simultaneous elimination of *other metabolic* functions is responsible for the fact that the hypopituitary patient (especially in the younger age groups) does comparatively well in *spite of cortical hypofunction. It is* almost certain, furthermore, that some cortical activity persists, even in patients with complete anterior-lobe failure.

(9) PRIMARY HYPOPLASIA of the adrenal cortex has been held responsible for certain types of alleged corti*cal insufficiency, known as "status thy*mico-lymphaticus" However, the very existence of this latter syndrome is somewhat in doubt.

(10) REPLACEMENT OF CORTICOID-PRODUCING, BY TESTOID-SECRETING TISSUE is another possible, though uncommon, cause of adrenal insufficiency

INCIDENCE

Although exact figures are difficult to obtain, the general incidence of frank Addison's disease is very low, according to the U. S Bureau of Statistics : 0.3 per 100,000 and about 16 cases per 100,000 admissions in the *Mayo Clinic. On the other hand,* the various forms of "addisonism" are fairly common complications of infections, intoxications and other *exhausting diseases*.

The disease may occur at any AGE, but is probably most common during the third decade Children are comparatively rarely affected and in them, the disease tends to take a chronic, benign course with predominance of gastro*intestinal symptoms* and pigmentation. Sometimes, however, acute forms of Addison's disease develop in the very *young, as a result of adrenal hemor*rhages, to which infants seem to be especially predisposed.

Addison's disease also occurs in very old patients, in whom the diagnosis is often difficult, because of the great resemblance of hypocorticoidism to senile marasmus.

The male SEX is more frequently affected by frank Addison's disease, especially among patients less than 45 years of age Only the hypocorticoid-

The blood LACTIC ACID content of addisonians rises markedly following, even mild, muscular exercise.

LIPID METABOLISM is less characteristically influenced by hypocorticoidism, although there is a great tendency to loose body fat and the blood cholesterol concentration tends to be low

The most prominent changes in PROTEIN METABOLISM are, a tendency towards an increase in blood urea and total N.P.N., with creatinuria. Unless adequate corticoid therapy is administered, the nitrogen balance becomes negative.

A rise in the organic, non-protein sulfates of the blood, presumably glutathione, has also been noted in addisonians.

Among the disturbances in WATER AND SALT METABOLISM, the most prominent are, a decrease in serum sodium and chloride, accompanied by an increase in serum potassium. At the same time, there is a diminution in the urinary excretion of potassium, accompanied by a slight but continuous rise in the sodium chloride elimination

The kidney, like the rest of the organism, loses its power of adaptation. Indeed, the outstanding renal defect is lack of adaptability to changes in intake of Na, Cl, K and water ("Fixed concentration"). High intake is followed by delayed excretion Low intake is followed by comparatively high excretion of Na, Cl and probably also of water

The negative NaCl balance is due to continuous losses. If large doses of NaCl are given (even without desoxycorticosterone) edema ensues

Eventually there is a decrease in blood volume and hemoconcentration These changes are finally accompanied by a diminished urine secretion, which terminally may become actual anuria

All these derangements in water and salt metabolism respond rather well to treatment with sodium chloride, cortical extracts or mineralo-corticoids such as desoxycorticosterone acetate. Excessive treatment with this steroid tends to produce edema, more readily in addisonians than in normal individuals.

The ALKALI RESERVE and the total base content of the blood are below normal in most patients suffering from Addison's disease.

It is noteworthy that many of the blood-chemical changes become severe only during the crises, while in the interim, the blood Na, K, Cl, CO_2-combining power, glucose and urea may remain within normal limits.

Growth and Bone Structure. — Contrary to expectations, if Addison's disease develops in children, the growth of the long bones is usually not very appreciably retarded. In adults, there is no great tendency to develop osteoporosis

Blood Picture. — It is of historic interest that Addison himself, classified his disease among the ANEMIAS. This is perhaps not entirely justified, but a decreased red cell count and hemoglobin concentration is frequent in addisonians It is perhaps partly due to the accompanying cachexia. Only if the hemoconcentration is very severe, does the loss of plasma fluid over-compensate for the diminution in red cell number

Usually, there is LYMPHOCYTOSIS and this is not accounted for by accompanying tuberculosis; it occurs even if the underlying cause is adrenal sclerosis with atrophy. Yet sometimes the lymphocyte count is normal, or even subnormal, in Addison's disease

Cardiovascular System. — The "remarkable feebleness of the HEART'S action," as described by Addison, is especially noticeable on auscultation An accompanying diminution in cardiac size is noticeable in X-ray pictures and by percussion. Autopsy reports reveal that the smallness of the heart is large-

(6) Decrease in blood volume.

(7) Hypoglycemic attacks.

(8) Disturbances in electrolyte metabolism.

(9) A great decrease in general resistance to any type of stress (e.g., intercurrent infections, intoxications, trauma, excessive muscular fatigue, extremes of temperature, malnutrition, administration of drugs, especially thyroid hormone, insulin, drastic laxatives, barbiturates, morphine).

It is important to remember that resistance and adaptation to stress, require much more cortical hormone than the mere maintenance of life Hence, if addisonians are exposed to strain, a so-called "addisonian crisis" may be elicited *and this is usually fatal*, unless drastic therapeutic measures are rapidly introduced.

During the crisis, there is a severe aggravation of the symptoms and signs, especially of the muscular asthenia (which renders the patient bedridden), the gastrointestinal disturbances, nausea and vomiting, hypotension (which may lead to anuria), psychic and nervous disturbances (e.g., headaches, hallucinations, deliria, melancholia or mania, convulsions, photophobia, cutaneous hypersensitivity), dehydration, hypoglycemia (which is frequently the immediate cause of death), a drop in blood pressure, body temperature, blood sodium and chlorides, a rise in blood potassium and N P N.

Depending upon the relative prominence of one or the other of these manifestations during the crises, the evolution of the disease may take any of the forms described in the *classification* of the primarily acute types of Addison's disease (see . Classification).

Metabolism. — The BASAL METABOLIC RATE (B M R.) is, often *but not* always, subnormal and rarely falls to the extraordinarily low levels characteristic of hypothyroidism or severe pituitary failure.

The BODY TEMPERATURE may be a few degrees below normal, but only during severe crises is there any pronounced hypothermia. It is rather characteristic of addisonians that if they contract infectious diseases, which normally would produce marked fever, they merely react with a slight rise in temperature and, indeed, if the infection elicits a crisis, the body temperature may actually fall. On the other hand, the crisis may be associated with hyperthermia — which is a bad omen.

Addison's disease causes very prom*inent disturbances in* CARBOHYDRATE METABOLISM. The fasting blood sugar level is rarely higher than 60-70 mg.%; even lower values are found during the *crises*.

Oral *administration of glucose* reveals an increased carbohydrate tolerance, the alimentary hyperglycemic curve being very flat and followed by, often dangerously steep, secondary hypoglycemia.

The sensitivity to *insulin* is greatly increased and since even moderate doses may cause fatal hypoglycemia, diagnostic insulin-blood-sugar curves should only be done with great precaution, after having prepared to administer glucose and adrenaline, if necessary

Adrenaline generally fails to elicit marked hyperglycemia, because of the low hepatic glycogen reserves of addisonian patients.

Some of the corticoids, not only increase the fasting blood sugar, but, also prevent the hypoglycemic attacks, which are otherwise so readily provoked *in addisonians by exposure to* stress Only gluco-corticoids and the adrenal-cortical extracts which contain them, are active in this respect, *while desoxycorticosterone is not.* This is presumably due to the fact that only gluco-corticoids exert a favorable influence upon gluconeogenesis from en*dogenous sources*

velops gradually. Early in the course of the disease, it is obvious only upon muscular effort but later, fatigue and exhaustion are evident, even after the slightest movement. Finally, muscular debility becomes the cardinal symptom. *Like most of the manifestations of Addison's disease, the asthenia is subject to considerable fluctuation. In ambulatory patients, it is most pronounced in the early hours of the morning, perhaps because it is aggravated by orthostatic hypotension after rising.* Objective ergographic examinations show that the weakness is not purely due to mental causes. They also reveal that the actual muscular strength is not very markedly impaired, in fully rested individuals, but declines rapidly after a few contractions. In this respect, the ergographic tracings are very similar to those obtained in adrenalectomized animals or patients with myasthenia gravis. Possible pathogenic relations with this latter disease are suggested by the frequency of excessive thymus growth in both conditions. (*See : The Thymus.*)

Nervous System. — Although nervous *and mental symptoms may* be lacking, they are often quite prominent. *Frequently, there are* SOLAR CRISES *or* CELIAC NEUROSIS. They manifest themselves by : *acute pain in the celiac* region, accompanied by vomiting, diarrhea, pain *along the course of the aorta* and its sympathetic plexuses. This may be so severe as to resemble that of coronary thrombosis It has been claimed that pain in the abdomen is present in approximately half of the cases, particularly during crises. The pain has no special relationship to meals, it is usually dull and of paroxysmal *character. It may* be so intense that the patient screams with pain during *the spells and the abdomen* becomes rigid as in peritonitis Often the pain is situated in the loins on both sides, and occasionally it is transmitted to the legs.

MENTAL SYMPTOMS, especially sudden psychic disturbances, such as melancholia or acute spells of maniac excitement, are quite frequent. The ability of concentration and thinking also suffer, as part of the general *asthenia.* In women, acute delirium with maniac excitement, often coincides *with menstruation. Frequently* there is a compulsive craving for salt.

SPELLS OF DIZZINESS are chiefly due to arterial hypotension, as stated above. *That is probably why they are so common* in the morning, when the patient *gets out of bed and assumes the erect* position, which predisposes to cerebral anemia The fact that the blood sugar also tends to fall to its lowest levels during the night's fast, contributes, of course, to the morning malaise.

EPILEPTIFORM CONVULSIONS can be associated with the symptoms of a solar crisis or occur independently; they are possibly also of hypoglycemic origin.

The TENDON AND PUPILLARY REFLEXES are usually normal, although, in some cases, there may be a positive Babinski or "labil" *light* reflexes of the pupil, especially during a crisis.

Among the SENSORY disturbances are · paresthesias, hyperesthesia of the skin, and *photophobia.* (*See also* : Sense Organs, below.)

MORPHOLOGIC LESIONS IN THE NERVOUS SYSTEM are uncommon in Addison's *disease, although some investigators* claim to have seen degenerative *changes in the ganglia of the solar* plexus.

Sense Organs. — The acuity of HEARING is often decreased and sometimes there is tinnitus.

VISION may become blurred and since this has been considered as one of the manifestations of the general asthenia, it has been described as "adynamy of vision." It is probably also the result of hypoglycemia.

Sometimes, addisonians suffer from a constant salty TASTE in the mouth.

ly functional, and due to the decreased blood volume, but the actual weight of the heart is also diminished.

It is remarkable how rapidly the cardiac size of the addisonian increases under the influence of NaCl or desoxycorticosterone acetate therapy, which restores the blood volume, and because the heart is flabby, tends to dilate it.

There is a great tendency towards HYPOTENSION, although, in patients who previously suffered from hypertension, the blood pressure may remain high until shortly before death. As a rule, systolic pressure varies between 90 and 100, diastolic between 60 and 70 mm. of mercury. *This hypotension is largely responsible for the coolness of the body surface, the attacks of dizziness and many other characteristic manifestations of Addison's disease.* The hypotension is often orthostatic, being evident *mainly during erect posture.* Not infrequently, addisonians suffer from mild RAYNAUD'S DISEASE.

Lymphatic Organs. — The THYMUS, LYMPH NODES, TONSILS, LYMPHATIC ELEMENTS IN PEYER'S PLAQUES AND SPLEEN, tend to be large in addisonians. This is readily understandable if we remember that the physiologic and "accidental" involution of these tissues is inhibited by a lack of corticoids, yet it is striking to note their great development in emaciated addisonians, since with most other diseases which lead to loss of weight, the lymphatic organs are the first to involute.

The so-called, "STATUS THYMICOLYMPHATICUS" is a condition which has been much discussed in the literature. Its main characteristics are an excessive development of the thymus, tonsils and other lymphatic organs, with a concomitant "hypoplasia" of the adrenals. It is supposedly responsible for many cases of sudden death ("mors thymica") in apparently healthy, children or young adults *exposed to some* acute but minor stress, such as a cold bath, surgical *trauma, anesthesia or* psychic shock. Undoubtedly, the development of the thymico-lymphatic apparatus is enhanced by cortical hypofunction, which also greatly reduces resistance to sudden stress. However, many of the allegedly pertinent cases were not due to cortical insufficiency. The "hypoplastic adrenals" of many patients, described as belonging to this group, were actually normal in size, although much smaller than those of most other patients. It must be kept in mind, however, that if death is sudden, there is no time to develop the usual increase in adrenal size, which is part of the general-adaptation-syndrome elicited by most of the fatal diseases. Hence, the true normal size of the *adrenals is much smaller than had been* supposed, on the basis of measurements on average autopsy material. Great *caution should be exercised therefore,* before accepting a case as "status thymico-lymphaticus," without denying the possible existence of such a syndrome.

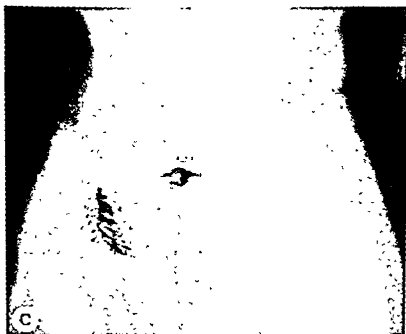
Respiratory Organs. — Even apart from the, often very mild (merely a Ghon tubercle), pulmonary tuberculosis, so frequent in addisonians, there appears to be a great sensitivity among them to various upper respiratory infections

The respiratory rhythm is usually very irregular during the crises (Biot's *type of respiration); there is dyspnea* and in the terminal stages the respiration may become extremely slow. Sighing *respirations,* on the other hand, are more common in psychoneurotics.

The VOICE is occasionally also altered and the speech may become difficult to understand, perhaps due to debility of the muscles involved

Muscles. — As already mentioned, asthenia, debility and languor are among the earliest symptoms of Addison's disease, although the histologic *structure of the muscles is essentially* normal. The muscular weakness de-





B. Spotty pigmentation of the lips and tongue — C. Pigmentation of appendectomy scar and linea alba (Cont d)

particularly marked Although the melanoderma tends to become more pronounced as the disease progresses it may improve during remissions

Patchy pigmentation of the mucous membrane within the mouth is not constant but when present it is of great diagnostic value It is seen on the lips,

which is probably due to atrophic glossitis. The resulting loss of appetite is largely responsible for the severe loss in body weight, so common in these patients.

Digestive System. — The prominent rôle played by the disturbances of the alimentary tract have already been mentioned in other connections. Usually there is nausea, sometimes accompanied by hiccups, gagging and occasionally intense diarrhea, but as a rule the patients tend more to constipation.

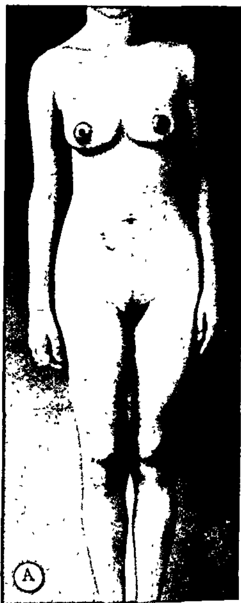
The symptoms of GASTRIC AND DUODENAL ULCERS may be super-imposed upon the ordinary signs of Addison's disease, although such ulcers usually occur only premortally.

GASTRIC ACIDITY fluctuates during the course of the disease, but tends to decrease whenever the condition of the patient becomes worse. Usually, the concentration of free HCl is reduced to 25-50% below normal and achlorhydria is common. This may be related to the disturbance in chloride metabolism, as mentioned above.

Function tests sometimes reveal slight disturbances in the activity of the LIVER, whose size is usually subnormal, but specific anatomic changes are rarely observed.

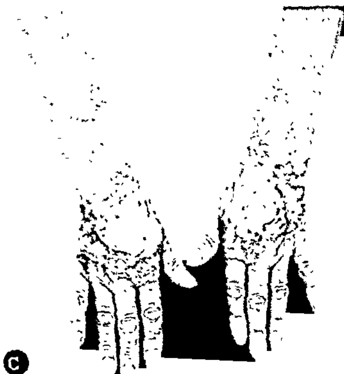
Skin. — The PIGMENTATION of the skin (melanoderma) and mucous membranes is one of the most characteristic symptoms of Addison's disease. It may develop very rapidly, but usually the acute cases of Addison's disease are conspicuous by the absence of excess pigmentation.

Melanoderma begins, and is usually most pronounced, in the wrinkles of the skin and in the parts exposed to light (e.g., hands, face) or pressure (e.g., under a tight garter, belt, collar, girdle, suspenders or studs). The tinge of the skin varies from that of a normal dark-skinned individual of the white race, to that of Arabians, Hindus



[illegible]

or even Negroes. Due to the accompanying anemia and hypotension the skin is rather grayish and dirty-looking. Usually, the discoloration is more or less diffuse, but jet-black lentigines and vitiligo-like, depigmented spots are also common. The pigmentation of the genital area and the nipples is





Pigmentation in Addison's disease. A. Pronounced *diffuse* melanoderma of the hands and black lentigines in Addison's disease — B. and C. Generalized pigmentation of the hands with vitiligo in Addison's disease — *D. Spotty pigmentation* of the scrotum in Addison's disease
(Courtesy of Dr E. J. Kepler)

D. Absence of axillary hair





(For legend of A and B see p 151)

function is frequently deficient. The specific gravity of the urine is low and excretion of ingested water and salt is delayed. (See also page 145.) Albumin is usually present in the urine, although often only in small amounts. Sometimes there are pus cells and erythrocytes, but these are usually due to concomitant kidney tuberculosis. The rise in blood N.P.N. and the terminal anuria are chiefly due to the fall in blood pressure, not to any primary kidney failure.

Sex Organs. — The MENSTRUAL CYCLE is sometimes disturbed, although amenorrhea is rare and menorrhagias tend to occur only in patients approaching the menopause. The manifestations of Addison's disease are often exacerbated during menstruation.

In the male, a tendency to loss of libido and IMPOTENCE are not uncommon, but occasionally sex activity is maintained and patients of either sex may become the parents of normal children, in spite of manifest addisonian symptoms.

LACTATION is rarely possible in addisonian women.

COMPLICATIONS

Among the complications of Addison's disease, the manifestations of an underlying TUBERCULOSIS, (often pulmonary, renal, osseous or "healed" visceral), SYPHILIS or CARCINOMATOSIS are most important. As mentioned above, the underlying destruction of the adrenal, is frequently due to a local focus of these diseases. Of course, if the causative, primary, systemic malady progresses, its own manifestations can complicate suprarenal insufficiency

The most important and dangerous complication of Addison's disease is the CRISIS, which may be elicited by a number of non-specific strains, enumerated above. Among these, complicating respiratory infections, such as bronchopneumonia, as well as tonsillitis and dental sepsis are especially common. The patients do not tend to be particularly susceptible to other (e g., skin) infections, but any infection, once acquired, is poorly tolerated.

In addition to the complications of the disease, there are now appearing the complications of OVER-TREATMENT with desoxycorticosterone, such as: generalized edema, focal myocardial necrosis, arthralgias, arthropathies, pericarditis and possibly nephritis.

DIAGNOSIS

The diagnosis of Addison's disease is attended with great responsibilities, since it brands the patient as severely ill and permanently dependent upon expensive medical treatment. It is based upon:

(1) Clinical manifestations of corticoid hormone deficiency.
(2) Local signs of a lesion in the adrenal region.
(3) Specific adrenal-cortical function tests.
(4) Recognition of certain systemic diseases known frequently to affect the adrenals.
(5) Differential diagnostic considerations.

(1) Clinical Manifestations of Corticoid Hormone Deficiency. — Typical and fully developed Addison's disease is readily recognized on the basis of the symptoms and signs as described under . Clinical Course The progressive asthenia, accompanied by hyperpigmentation, gastrointestinal irritability and arterial hypotension, are of the greatest diagnostic value, especially if all of them are present However, even in the most typical case, it is advisable to confirm the diagnosis, by the signs and tests listed below.

(2) Local Signs of a Lesion in the Adrenal Region. — Radiologic evidence of calcification in the adrenal



Addison's disease
(After W M Yater Fundamentals of Internal Medicine Appleton-Century Publ 1944)
Pigmentation of lips and gums.

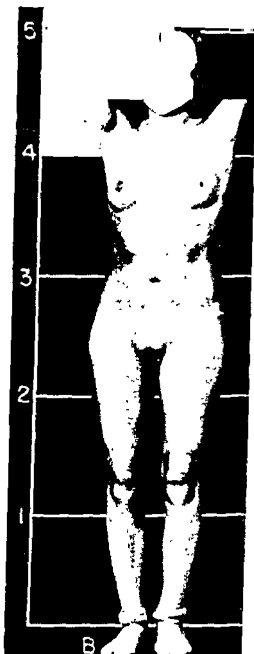
inner aspect of the cheeks, gums, hard palate and uvula. Even the margins *of the eyelids, the conjunctiva and the* limbus corneae may become pigmented The mucous membranes of the rectum *and vagina are rarely affected*

Histologically, the skin lesions are not diagnostic. As in sunburned patients, or those belonging to pigmented races, there is melanin deposition both in the epidermis and the cutis. Pigment granules are found throughout the epidermis, but are especially dense in the basal cells and in the tips of the rete ridges. The pigment deposition is chiefly intracellular. It is noteworthy that although corticoid treatment may improve the melanoderma, it rarely affects it as much as the other manifestations of cortical insufficiency

The mechanism of pigment *formation* in Addison's disease has still not been clarified, but Bloch claims that a specific oxydase *in the skin forms melanin* from dihydroxyphenylalanine (dopa). (See p. 109.)

Scanty HAIR growth, *and* especially loss of axillary and pubic hair are rather characteristic

Urinary System. — The KIDNEY rarely shows any characteristic structural changes, although nephrosis with *tubular* atrophy and renal tuberculosis are often found in addisonians Renal



Addison's disease
(After Albright et al Am J Med Sc 204 625 1942)
Note complete absence of axillary and pubic hair, in spite of normal sexual development

from then on until and including 7:30 a.m., is collected. The volume of this urine is measured and the specimen saved for chemical analysis, if this should be necessary later. Breakfast is omitted. The patient is asked to void again at 8:30 a.m. and immediately thereafter he is given 20 cc. of water /Kg. of body weight (9 cc./pound). He is asked to drink this within the next forty-five minutes. At 9:30, 10.30, 11:30 a.m. and 12:30 p.m. he is requested to empty his bladder. In order to eliminate the effects of exercise and posture on urinary excretion, he is kept at rest in bed except when up to void. Each specimen is kept in a separate container. The volume of the largest one of these four specimens is measured.

Under these conditions some addisonians excrete so little urine that they are unable to void more than once or twice during the entire morning. In such instances, the amount of urine excreted per hour may be calculated, frequently, however, such calculations are unnecessary because of the very low total urinary output.

If the volume of any single hourly specimen, voided during the morning, is greater than the volume of urine voided during the night, the test is negative, that is, it indicates absence of Addison's disease. If the volume of the largest hourly specimen voided during the morning, is less than the volume of urine voided during the night, the test is positive, but indicates only the possible existence of Addison's disease. In such instances, procedure 2 should be instituted to establish the diagnosis.

Procedure 2 (based on blood and urine chemistry). — To proceed with this test, blood is drawn (preferably under oil), while the patient is still fasting, and the urea and chloride contents are determined in the plasma and in the night urine specimen. From these four determinations and from the results obtained from procedure 1, the following equation is solved :

$$A = \frac{\text{Urea in urine (mg.\%)}}{\text{Urea in plasma (mg \%)}} \times \frac{\text{Chloride in plasma (mg.\%)}}{\text{Chloride in urine (mg \%)}} \times \frac{\text{Volume of day urine (cc.)}}{\text{Volume of night urine (cc)}}$$

The term "day urine" applies to the largest of the hourly specimens voided during the day; "night urine," to the entire amount which was voided from 10:30 p.m. to 7.30 a.m. It is immaterial how these values are expressed, provided that the same method be used throughout the equation. For example, if the concentration of plasma chloride is expressed as mg. of NaCl/100 cc the concentration of urinary Cl. should be expressed in the same manner.

It is considered that if the value of "A" is greater in the above equation than 30, we are not dealing with Addison's disease. If this value is below 25, the existence of Addison's disease is very probable if nephritis has been excluded. The test is most valuable if negative, since then it excludes Addison's disease with almost absolute certainty. A positive test nearly always means that the patient is severely ill but the hypocorticoidism may be relative rather than absolute (due to adrenal destruction) In doubtful cases a salt deprivation test is indicated

The Therapeutic Function Test is based upon the fact that administration of corticoid preparations is particularly beneficial if cortical function is deficient. A striking amelioration, in the clinical and laboratory manifestations of patients suspected of Addison's disease, following administration of corticoid therapy, may there-

region (the angle between the ribs and the 12th thoracic or 1st lumbar vertebra), is comparatively common, especially in those cases of Addison's disease which are due to tuberculosis. Air insufflation into the stomach (in the case of the left adrenal), or peritoneum facilitates radiography of the adrenal region. Some authors recommend perirenal air insufflation to produce a local emphysema, for the diagnosis of adrenal tumors, but none of these drastic procedures are permissible in the presence of untreated severe insufficiency. Large, palpable, destructive tumors, or signs of secondary invasion (e.g., hematuria) and displacement (detectable by palpation or radiography), with or without pyelography of the kidney, are comparatively rare. On the other hand, the rather common pain in the lumbar region is not very characteristic.

(3) Specific Adrenal-Cortical Function Tests. — These are based upon the inability of the hypocorticoid organism to respond normally to various types of stress

The SALT DEPRIVATION TEST (*Harrop* et al. 1933), consists of putting the patient on a sodium chloride-poor diet for three days. If obvious symptoms of acute adrenal insufficiency ensue, it is very probable that we are dealing with Addison's disease. The test is not without dangers, however, and since it is evaluated on rather subjective clinical grounds, it does not enjoy great popularity.

The POTASSIUM RESISTANCE TEST (*Cutler, Power and Wilder,* 1938), is performed by placing the patient on a sodium chloride-poor and potassium-rich diet. Chloride concentration in the urine is determined during the last four hours, in Addison's disease it is above normal. While the test is rather reliable, it has the disadvantage of involving considerable danger (even deaths have been reported), because of the great potassium sensitivity of the addisonians; false positives may occur in untreated diabetics and in certain types of renal disease.

The POTASSIUM TOLERANCE TEST (*Zwemer and Truszkowski,* 1936). This consists in the administration of potassium in the form of a function or tolerance test, with subsequent determination of the plasma potassium curve. A particularly steep hyperpotassemia is considered characteristic of Addison's disease. However, the test is dangerous and nephritis with edema, myasthenia gravis, malnutrition, neurasthenia and several other conditions may also decrease potassium tolerance sufficiently to give positive results.

The ROBINSON, POWER AND KEPLER TEST (1941), is regarded as a reliable function test and has the great advantage of not entailing any danger. It is based upon two facts :

(1) Following the rapid ingestion of a considerable amount of water, addisonians excrete the excess water much more slowly than normals, due to a diminished ability to produce a dilute urine.

(2) Addisonians tend to excrete excessive amounts of sodium and chloride, while retaining urea.

The test is sub-divided into two parts, to examine each of the above-mentioned disturbances separately. False positives are sometimes obtained in certain nephropathies, hyperthyroidism, and cachexia (relative hypocorticoidism ?). Because of its practical value, we shall describe this test in detail, quoting its originators almost verbatim ·

Procedure 1 (*based on urine volume*) *"The water test."* — On the day before the test the patient eats three ordinary meals, but omits extra salt. He is requested not to eat or drink anything after 6 p.m. Until then, he may drink water as desired At 10.30 p m he is requested to empty his bladder and discard the urine All urine which is voided

to the itching, are also of diagnostic value.

In PERNICIOUS ANEMIA, the skin coloration is often dark and, in view of the accompanying anemia, the diagnosis may be difficult unless adequate hematologic studies are performed. It is of historic interest that Addison himself considered the two conditions as closely related to each other.

CHLOASMA UTERINUM is accompanied by menstrual disturbances and since the latter are fairly common in addisonians, this possibility should not be left unconsidered.

TUBERCULOSIS leads to diagnostic difficulties, firstly, because tuberculosis is so common among true addisonians and secondly, because, even if the adrenals are not involved, such signs as pigmentation, disturbances in the sex organs, arterial hypotension and severe asthenia with gastrointestinal manifestations, are often observed in tubercular individuals. Pain, or radiologically detectable calcification in the suprarenal region, is usually indicative of suprarenal involvement.

In MALARIA the antecedents, the characteristic fever, splenomegaly and the demonstration of the parasites in the blood will facilitate the diagnosis *in spite of the* pigmentation. It must be remembered, however, that a functional adrenal failure, with addisonian symptoms, is not uncommonly associated with malaria.

The cutaneous hyperpigmentation in SYPHILIS is usually restricted to certain regions, such as, the back of the neck and the shoulders. Furthermore, there are no other accompanying manifestations of Addison's disease and the serologic reactions facilitate the diagnosis, even if asthenia and arterial hypotension are present, as is frequently the case in chronic syphilitics. This differential diagnosis is of importance because of the frequent association of syphilis with true Addison's disease, due to secondary involvement of the adrenals.

Among other conditions, likely to cause diagnostic difficulties, early LIVER CIRRHOSIS, HYPERTHYROIDISM with pigmentation, ANOREXIA NERVOSA and CHRONIC NERVOUS EXHAUSTION, should be considered.

Exploratory *skin biopsies* are of value in the recognition of certain types of melanodermas, for instance, those of acanthosis nigricans and metal poisonings, but they should not be performed, without previous corticoid treatment, since untreated addisonians are so very sensitive to any type of surgical intervention and the accompanying excitement.

PROGNOSIS

The prognosis of FRANK ADDISON'S DISEASE is always very grave. While the introduction of sodium chloride and especially of corticoid hormone therapy has greatly improved the chances of prolonged survival, it must be kept in mind that in a very large percentage of the cases, the adrenal destruction is merely one manifestation of such serious systemic diseases as tuberculosis, syphilis, carcinomatosis, etc. These, in themselves, are often fatal, if they *reach a stage where secondary deposits* destroy the adrenals. But even when Addison's disease is due to a primary adrenal failure, or if the basic disease is under control, the prognosis is poor, because it is extremely difficult to supply adequate therapy for all the contingencies of normal life Any accidental interruption of the therapy, or any intercurrent stress, may be fatal unless immediately met by an appropriate increase in corticoid hormone administration. Hence, the average life span of the addisonian still rarely extends over more than a few years.

On the other hand, the so-called "FORMES FRUSTES," or cases of CONSTITUTIONAL ADDISONISM, due to tem-

fore also be used, as an innocuous and rather specific function test, among other diseases. Only secondary hypocorticoidism, due to anterior-pituitary deficiency, is likely to respond with an almost equally dramatic improvement. *It is well to bear in mind, however, that purely subjective improvement is of no diagnostic value.*

Other Laboratory Tests. Among other laboratory tests designed to reveal derangements, which are more or less specific of hypocorticoidism, the following are worth mentioning:

(1) Severe fasting hypoglycemia.
(2) Increased glucose tolerance, with severe secondary hypoglycemia after ingestion of sugar.
(3) Extraordinarily severe *hypoglycemia following insulin* administration (dangerous!).
(4) High plasma potassium values.
(5) Low plasma sodium and chloride values.
(6) Negative NaCl balance.
(7) Markedly diminished 17-KS. elimination in the urine. (Very low in females, about half of normal in males.)
(8) Increased blood N.P.N. and blood urea.
(9) Achlorhydria.
(10) A diminished B.M.R. in the absence of hypopituitarism or hypothyroidism.
(11) Increased blood CO_2 capacity.
(12) *Hemoconcentration* with decreased blood volume.

(4) Recognition of Certain Systemic Diseases Known Frequently to Affect the Adrenals. — As we have repeatedly said in other connections, tuberculosis is one of the most common causes of adrenal destruction and hence, the recognition of tuberculosis, in any organ, raises the suspicion of Addison's disease, if signs of probable hypocorticoidism are also present. The same is true, to a lesser degree, of syphilis, carcinomatosis, and some exhaustive acute diseases (influenza, puerperal infections), which *are likely to cause secondary exhaustion atrophy of the adrenals.*

(5) Differential Diagnostic Considerations. — *Confusion* with melanoderma due to solar or X-ray irradiation, *as well as that produced by exposure to heat,* is readily eliminated by the past history of the patient. Pigmentation induced by various skin ointments and lotions (especially ointments containing mercury), is limited by the regions treated. Racial melanoderma may cause diagnostic difficulties, since it is sometimes not easy *to estimate the degree of skin pigmentation,* which could be called pathologic in pigmented races. Here again, a history of a sudden unexplained increase in the darkness of the skin, as well as the absence of the characteristic pigmentations and jet-black lentigines are significant. Metallic poisoning, especially with lead, arsenic, bismuth or silver, must also be excluded, by an inquiry into the past history and a search for other manifestations of these intoxications. In acanthosis nigricans, the pigmented areas are usually axillary and of velvety appearance, rather than of the satin-like type, typical of Addison's disease. *Hemochromatosis may be recognized* by the demonstration of iron pigment in the skin, the presence (in the late stages) of *sugar in the urine and an* enlargement of the liver. The ordinary liver function tests, however, usually give normal values. *Scleroderma is* frequently accompanied by melanoderma, suggestive of Addison's disease, but its symptoms and signs are so characteristic that confusion will rarely occur. Carotenemia and jaundice are recognized by the presence of the abnormal pigments in the serum. Pregnancy may lead to hyperpigmentation. The same is true of "vagabonds' disease" but here, the skin scratches due

ministered in small portions, than if given in a single large dose Certain lipid-soluble extracts (e.g., Upjohn's lipocortical extract) are about five times as active as the usual aqueous solutions and require only one injection per day because of delayed absorption. Since for most patients, the cost of prolonged treatment with cortical extract is still prohibitive, there is a tendency to use an insufficient dosage.

Corticoid extracts or adsorbates of cortical material to charcoal given orally, are much less effective in clinical medicine, although in some animal species, corticoids are highly active by mouth.

Among the chemically pure cortical steroids, only DESOXYCORTICOSTERONE ACETATE is commercially available in adequate quantities at this time. Its chief advantage is its comparatively low price. Its main disadvantage is that, when given in high doses, it is toxic. It may cause a marked increase in blood volume, edema with anasarca, arterial hypertension, cardiac insufficiency, angina-like pain, nephrosclerosis with proteinuria, dyspnea, profound muscular weakness, arthralgias, and a dangerous degree of hypopotassemia. However, these toxic manifestations rarely occur with the minimum therapeutic doses and hence, under constant supervision, the hormone may be used to advantage. Unfortunately, desoxycorticosterone acetate is practically devoid of gluco-corticoid activity Hence, patients otherwise adequately treated with this steroid may develop dangerous, sometimes fatal, addisonian hypoglycemia with asthenia, even if the other symptoms and signs of hypocorticoidism are completely prevented Hypoglycemia may occur even in patients who simultaneously show marked signs of desoxycorticosterone intoxication.

In general, daily doses of 2 to 6 mg. of desoxycorticosterone acetate are sufficient when given subcutaneously, intramuscularly or by the sublingual route. The latter mode of application is especially recommended. The subcutaneous implantation of compressed desoxycorticosterone acetate tablets is also effective, it is not recommended, however, since dosage cannot be adjusted to changing requirements. Many patients can be maintained for months, or even years, with no other hormone therapy but desoxycorticosterone acetate. They should constantly be checked, however, for danger signals of overdosage or hypoglycemia. Their vigour and well-being may also be improved by simultaneous treatment with *testoids* (e.g., 30 mg. methyl-testosterone per day), in both sexes.

Since SODIUM CHLORIDE is particularly beneficial to hypocorticoid patients, their diet should contain a fair amount of salt. If corticoid preparations are unavailable, even mere salt therapy may suffice to control the manifestations of insufficiency. Conversely, no extra salt may be necessary if the patient can afford adequate doses of desoxycorticosterone. Na-citrate or bicarbonate are even more effective than NaCl, but usually salt therapy is employed in combination with cortical extracts or desoxycorticosterone. In the food, NaCl should be given only in quantities which are considered necessary to season it, otherwise, the already poor appetite of the addisonian may be adversely influenced. In addition to this, NaCl tablets containing 0.5 to 1 0 gm each should be prescribed.

If these are badly tolerated, the following drink is recommended by some (*Del Castillo et al*)

Sodium chloride	10 gm
Sodium citrate	5 "
Glucose	160 "
Fruit juice (lemon)	80 cc

Add water to bring total volume to one liter

Some patients prefer taking this drink (chilled), to the sodium chloride tablets, but it may

porary, functional failure of the cortex, frequently end in complete recovery, even without therapy. *In any event,* their rational treatment is stimulation of the adrenal cortex (corticotrophins) rather than replacement therapy with corticoids, which tend to cause compensatory cortical atrophy and overdosage symptoms.

A large number of addisonians succumb due to overtreatment with desoxycorticosterone and NaCl, especially since the symptoms of this overdosage resemble those of the addisonian crisis (weakness, hypoglycemia), hence, the physician without adequate laboratory facilities tends to meet them by a further increase in desoxycorticosterone and NaCl therapy.

THERAPY

The treatment of Addison's disease may conveniently be discussed under the following headings:

(1) Treatment of the underlying disease responsible for the adrenal destruction.

(2) Treatment of the manifestations of hypocorticoidism.

(3) Treatment and prevention of the addisonian crisis.

(1) Treatment of the Underlying Disease Responsible for the Adrenal Destruction. — *If* TUBERCULOSIS *occurs* in combination with Addison's disease *it is almost invariably the cause of the* latter In such instances, the systemic *tuberculosis should be treated in accordance* with generally accepted *therapeutic principles.* A detailed discussion of *these would be beyond the* scope of this book

Essentially the same is true as regards SYPHILIS and MALARIA. In some pertinent cases adequate antisyphilitic or antimalarial therapy led to a permanent cure of hypocorticoidism

If HYPOPITUITARISM is accompanied by especially severe manifestations of adrenal-cortical hypofunction, the rational *therapy would consist in the* administration of purified adrenocorticotrophic hormones. *Such preparations* are not as yet commercially available in adequate *quantities and since hypo*corticoidism of pituitary origin responds well to the usual *corticoid and* salt therapy, as discussed below, it is justified to treat these cases *as if they* were primarily due to cortical malfunction.

It should also be kept in mind that hypopituitary patients suffer from a complex hormonal disturbance and that even if the cortical deficiency is most prominent in the syndrome, the other hormonal derangements should also be treated. Hence, it is advisable to handle such patients in agreement with the principles enumerated in the section on the therapy of hypopituitarism

(2) Treatment of the Manifestations of Hypocorticoidism. — Since purified natural corticoids are not yet commercially available in adequate quantities, the most effective practical therapeutic procedure is to administer ADRENAL-CORTICAL EXTRACTS *several* times a day subcutaneously, intramuscularly or, in the case of imminent danger, intravenously The degree of purity and the potency of the various extracts is rather variable, but the average active preparation, now on the market, can be administered in almost any quantity without having to fear overdosage phenomena Anywhere between *2 to 100 cc per day may be nec*essary to keep the patient free of *deficiency symptoms.* The daily dose *should be subdivided into several in*jections, given at regular intervals Under basic conditions, two daily injections suffice but during exacerbations, injections may be necessary every six, or even every three hours, throughout the day and night. Fractionation of the dose is essential, because the effect is very transitory and a given amount is much more effective if ad-

intravenously, as well as 1.5 liters of a 10% glucose solution. Each of these infusions should contain at least 25 cc. of cortical extract and in addition, 25 cc. may be given intramuscularly. If the patient is moribund 200-300 cc. of extract may be necessary. (In view of the comparatively slow activity, and dubious gluco-corticoid potency, of desoxycorticosterone acetate, it is not recommendable during the crisis.)

Unless the condition of the patient has advanced to an irreversible stage, improvement is almost instantaneous. However, intense sodium chloride, glucose and corticoid hormone therapy must be continued, together with the administration of large amounts of fluid, until the patient has definitely passed the critical period. If these precautions are observed, it is often possible to save the patient even in advanced stages of a crisis, when therapeutic measures were invariably futile before the discovery of the corticoids. In very advanced cases, however, the condition becomes irreversible and cannot be improved by any known therapeutic procedure. Occasionally, recovery from a crisis is followed by permanent damage to the nervous system (loss of memory, mental deficiency etc.), reminiscent of that which tends to occur after insulin shock.

HYPERCORTICOIDISM

(SYNONYMS: hyperadrenalism, hyperadrenia; when combined with pseudohermaphroditism: adrenogenital syndrome of Cooke-Apert-Gallais, suprarenogenital syndrome of Kraus, hirsutism of Apert, adrenal-hermaphroditism, adrenal virilism; when accompanied by precocious sexual development in children: macrogenitosomia precox suprarenalis; when accompanied by glycosuria in women: diabetes of bearded women, Achard-Thiers syndrome.)

DEFINITION

Hypercorticoidism is a condition in which the hormone production of the adrenal cortex is sufficiently augmented to cause detectable overdosage manifestations.

It must be kept in mind that the adrenal cortex produces a number of hormones with qualitatively different properties. Since, under certain conditions, the excess production of one or the other of these substances may prevail, it is obvious that hypercorticoidism can manifest itself in a variety of clinical forms. We shall elaborate further on this point in the chapter on Classification. It may appear somewhat artificial to group together, under the generic designation of hypercorticoidism, such a heterogeneous group of diseases as we shall find in this chapter. Yet, since they are all due to excessive function of adrenal-cortical cells, their conjoint discussion is justified.

CLASSIFICATION

It is rather difficult to find a satisfactory basis for the classification of clinical hypercorticoidism. Theoretically, there could be one clinical overdosage syndrome corresponding to each of the cortical steroids, which possess qualitatively different actions. Thus, there could be syndromes characterized by virilization (adrenal testoids), feminization (adrenal folliculoids and luteoids), diabetes (gluco-corticoids), hypertension and nephrosclerosis (mineralo-corticoids), and perhaps even syndromes specifically due to overdosage with "lipo-corticoid" (?) and anesthetic steroids. Actually, most cases of hypercorticoidism exhibit a mixed symptomatology. This is perhaps due, partly to the fact that usually several corticoids are simultaneously

be poorly tolerated, although this is rarely the case in patients who really need salt therapy.

In times of danger, the subcutaneous, or even intravenous, administration of hypertonic sodium chloride solution may be necessary.

In patients receiving desoxycorticosterone, the necessary total daily dose of NaCl varies between 3 and 5 gm. in addition to what is taken with the diet. Somewhat higher doses are recommended in the absence of corticoid therapy (e.g., 10 gm. of NaCl and 5 gm of Na-citrate).

In prescribing NaCl, it must be kept in mind that its chief advantage is to increase the efficacy of corticoids, but it also augments their toxicity.

In view of the great progress made in the extraction and synthesis of gluco-corticoids, it is most probable that these will be available for clinical use within a short time. This could hardly fail to improve the therapy of Addison's disease. At the present time, however, the combined salt and corticoid therapy, as described above, is still the best practical procedure.

In view of the great tendency of addisonians (even those treated with desoxycorticosterone acetate) to develop dangerous hypoglycemia, (especially before breakfast or during anorexia), it is well to administer a high CARBOHYDRATE diet in the form of foods rich in starch and sugar, supplemented by fruit juices, containing as much glucose as the patient can take without spoiling his appetite

Since POTASSIUM salts are extremely toxic to addisonians, if tolerated, the diet should not contain more than 2 gm. of potassium, per day. This greatly increases the efficacy of salt or corticoid therapy but, in patients treated with desoxycorticosterone acetate, care must be taken not to reduce the dietary potassium too far, as this increases the danger of hypopotassemia Some addisonians are extremely sensitive to, even small doses of, desoxycorticosterone acetate (0.5-1.0 mg), perhaps because in them the hormone tends to deplete the potassium stores without correcting the other manifestations of hypocorticoidism. Since low potassium diets are unpleasant, and reduction of dietary potassium is not necessary in the presence of adequate corticoid therapy, low K diets have been discarded in most clinics.

It is also important to ascertain that the patients continuously take CALORICALLY ADEQUATE AMOUNTS OF FOOD, especially that their evening meal be sufficiently substantial to prevent fasting hypoglycemia during the night and that they receive a minimum maintenance amount of PROTEIN and VITAMINS

(3) Treatment and Prevention of the Addisonian Crisis. — Addisonians must take special care to AVOID STRESS OR STRAIN, such as: excessive muscular exercise, exposure to cold, exposure to the danger of intercurrent, respiratory infections. In view of the great sensitivity of addisonians to insulin, thyroid hormone, barbiturates and morphia, these drugs should be given only if absolutely necessary. The same is true of surgical interventions. If exposing an addisonian to one or the other of these agents is unavoidable, the corticoid therapy should be preventively increased Thus, two or three days before an unavoidable surgical intervention, large doses of sodium chloride should be given in combination with much more than the normal maintenance dose of cortical extracts Just before the surgical intervention, about two liters of a saline-glucose solution with 50 cc. of the usual potent commercial cortical hormone extract should be given slowly, intravenously. In adequately treated patients, Addison's disease is no longer a contraindication, even for severe surgical interventions if they are really necessary.

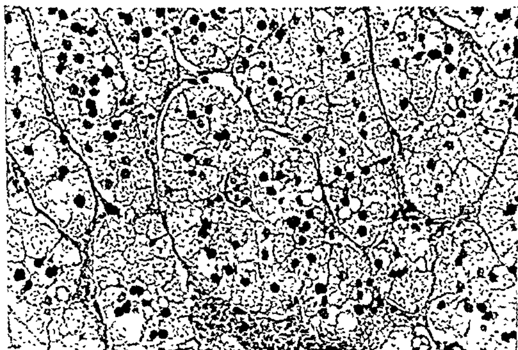
If a CRISIS ENSUES, the patient is immediately put to bed and kept warm. During the first day, it is advisable to administer one liter of 1 5% NaCl,

genital syndrome, simple hyperplasia of the cortex is the only detectable adrenal change. It has been claimed that in such cases, the cortex shows histologic characteristics typical of the suprarenogenital syndrome. Thus, *Broster and Vines* (1933) emphasized that in virilism certain cortical cells show a special affinity for ponceau fuchsin, even if no enlargement of the gland is observed. Others (*Goldzieher and Koster*, 1935), claim that hyperplasia and marked eosinophilia of the zona reticularis is a constant finding in adrenal virilism with adiposity, even if there is no marked increase in the total size of the cortex. As has been stated in other parts of this chapter, experimental work also suggests that this zone (which corresponds to the X-zone), is particularly concerned with the elaboration of adrenal testoids

Enlargement of Accessory Adrenal-Cortical Tissue. — This may take the form of the so-called "hypernephroma of the ovary" or may be due to hyperplastic cortical cell nodules in the mesovarium, the spermatic cord or other ectopic sites.

Cortical Adenomas. — The often multiple and minute, usually subcapsular, cortical adenomas, are frequently designated as nodular hyperplasia of the cortex They rarely manifest signs of hypercorticoidism. However, single or multiple large adenomas are often conductive to the adrenogenital syndrome. The histologic structure of these neoplasms does not differ essentially from that of hormonally inactive cortical adenomas, or those merely associated with hypertension, without pseudohermaphroditism (See also p. 190.)

Cortical Carcinomas. — The differentiation of the true adrenal-cortical carcinoma from the Grawitz' tumor or "hypernephroma" is discussed in connection with the adrenal tumors. Suf-



Adenoma of the adrenal cortex. Note typical appearance of light, vacuolated (lipid-containing) cortical cell trabeculæ

(Courtesy of Dr P Masson).

produced in excess and partly, to the manifold biologic activities of individual steroids. The existence of pure, uncomplicated diabetes or renal hypertensive disease, secondary to hypercorticoidism, has not yet been definitely proven. Although there is a good deal of evidence indicating that such syndromes and a variety of "Diseases of Adaptation" (see corresponding section) occur as a result of hypercorticoidism, we shall limit ourselves here to a discussion of the so-called adrenogenital syndrome, whose dependence upon hypercorticoidism has been demonstrated beyond doubt.

According to the AGE OF ONSET we distinguish between :

(1) Adrenogenital syndrome *in the fetus*, with pseudohermaphroditism in females.

(2) Adrenogenital syndrome *in children* .

  (a) Precocious puberty, with pseudohermaphroditism in females.

  (b) Precocious puberty, without pseudohermaphroditism in females

  (c) Precocious puberty, without pseudohermaphroditism in males

(3) Adrenogenital syndrome *in adults*

  (a) With pseudohermaphroditism in women.

  (b) With pseudohermaphroditism in men

The pseudohermaphroditic development of the sex organs is much more common in females and most pronounced if the disturbance commences, at an early age, at least before the advent of puberty.

According to the INTENSITY of the clinical manifestations, we may distinguish :

(1) Adrenal pseudohermaphroditism with marked heterosexual differentiation.

(2) Simple virilization or *feminization*.

According to the UNDERLYING ADRENAL LESION, it is customary to distinguish :

(1) Simple hyperplasia of the adrenal cortex.

(2) Enlargement of accessory adrenal-cortical tissue.

(3) Cortical adenomas.

(4) Cortical carcinomas.

In all these types, symptoms of Cushing's syndrome (see : Diseases of the Hypophysis) may be superimposed.

It should be emphasized that, in the earlier literature, pseudohermaphroditism was regarded as a congenital malformation of the accessory sex organs, which caused them to assume characteristics of the sex opposite to that of the patients' gonads These conditions are fulfilled, at least in the most precocious types of the adrenogenital syndrome. We know now that, both the embryonic and postnatal differentiation of the accessory sex organs is regulated by hormones and that these can direct it either in the normal or heterologous sense. No known facts indicate that genetically-conditioned malformations can accomplish this without the intermediary of hormones. Hence, it appears appropriate to include the heterologous differentiation of adrenal origin as one of the types of pseudohermaphroditism.

PATHOLOGIC ANATOMY

Some of the adrenal lesions, which can cause hypercorticoidism, such as cortical hyperplasia (see . Malformations on p 136) and cortical tumors (see p. 190), have been discussed in other parts of this chapter. Hence, here we shall consider only those morphologic alterations which are most characteristic of the adrenogenital syndrome in particular

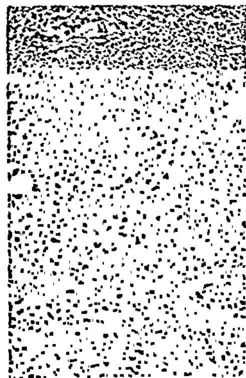
Simple Hyperplasia of the Adrenal Cortex. — In many instances of adreno-

fice it to say here, that the more anaplastic the cortical carcinoma, the less likely it is to produce hormone overdosage symptoms. As in the case of the adenomas, those cortical carcinomas, which are conducive to hypercorticoidism, reveal no morphologic characteristics permitting the recognition of their functional activity.

In exceptional cases, an adrenal carcinoma, which originally caused hypercorticoidism, eventually destroys the adrenal and after metastasizing into the contralateral gland, results in the destruction of all functional tissue. In such instances, not only do the manifestations of hyperactivity disappear, but, secondary addisonism ensues. This phenomenon occurs more often as the result of hyperplasia of the testoid-producing, at the expense of corticoid-secreting adrenal tissue. In very young infants it may cause death, even before the sexual changes have had time to appear. In one case (*Kepler*), the child did not die because of replacement therapy and she subsequently showed signs of adrenal virilism. The clinical picture in these cases suggests pyloric stenosis

It is of practical importance that a hyperactive, unilateral, cortical neoplasm, whether an adenoma or a carcinoma, usually causes severe compensatory atrophy of the contralateral gland. Hence, severe and often fatal adrenal insufficiency may ensue after extirpation of the tumor, unless the patient is preventively treated with adequate amounts of corticoid preparations. (See also p 191)

Other Diseases. — There is some disagreement regarding the adrenal changes in renal HYPERTENSION and NEPHROSCLEROSIS. Some investigators claim that signs of diffuse or nodular hyperplasia are more common in this disease than in the average autopsy material; others deny this It is certain that renal hypertension is usually not accompanied by as marked cortical lesions as the adrenogenital syndrome Yet, in several clear-cut cases, cortical tumors or hyperplasia were accompanied by hypertension, nephrosclerosis or periarteritis nodosa and in some of these, removal of the proliferating cortical tissue had a curative effect. Experimental work (see pages 122 and 125), also suggests that the adrenal cortex plays an important part in the pathogenesis of renal hypertension. It is probable, therefore, that the lack of morphologic support for this interpretation is mainly due to our inability to recognize the histologic changes underlying certain types of function. It will be recalled that the fuchsinophilia of the reticularis in virilism likewise remained unrecognized until the discovery of its special staining qualities



Carcinoma of the adrenal cortex. Very atypical [illegible]

A

B

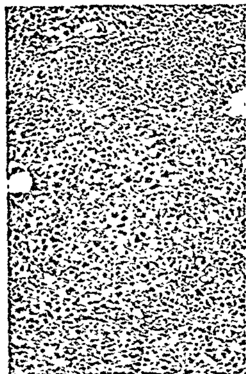
Carcinoma of the adrenal cortex. Girl, age 4 years, with metastasizing cortical carcinoma. — A. Primary tumor, with giant cells and very atypical polymorph cellular structure. — B. Section from a pulmonary metastasis of the same tumor. Note that the structure is very similar to that of the primary tumor. (Courtesy of Dr. P. [illegible].)

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Carcinoma of the adrenal cortex. Very atypical carcinoma of the adrenal cortex, with numerous giant cells and highly irregular nuclei Compare with the small cellular trabeculæ of the normal adrenal cortex near the periphery of the field.

INCIDENCE

The GENERAL INCIDENCE of the fully developed adrenogenital syndrome is very low. Mild types of virilism, on the other hand, are so *common among* women that they may even be regarded as being on the borderline of the normal. *In most of the mild cases, it is difficult* to ascertain the adrenal origin of the manifestations and hence, *statistical studies* are almost impossible.

The general incidence of hypertensive disease and other "diseases of adaptation" is probably the highest of all maladies of man, but it is yet to be determined what percentage of the relevant cases are due to hypercorticoidism.

While the adrenogenital syndrome may develop at any AGE, the characteristic, severe cases are most common among children This may be due, at least partly, to the greater ease with which pseudohermaphroditic changes develop at a time when the sex organs are still incompletely formed. Comparatively mild virilism (especially hirsutism), on the other hand, is very common among postmenopausal women, and there are good reasons to believe that this is of adrenal-cortical origin It is frequently accompanied by hypertension and sometimes by increased urinary 17-KS excretion. The terms, "postmenopausal virilism" or "postmenopausal Cushing's syndrome" have been coined to *designate* relevant cases. Some authors think that after the menopause, the diminution of female sex *hormone production may* be conducive to an increased pituitary adrenotrophic hormone secretion and secondarily to *signs of* hypercorticoidism This theory is yet to be proven, especially since some of these changes may be due to *anomalies* of the end-organs, rather than to endocrine derangements. It is almost certain that such a mechanism is *operative* in the beardless Chinese and American Indian males

The female SEX is about five times more frequently affected than the male.

HEREDITY also plays an important rôle in the pathogenesis of the disease. In many instances, the adrenogenital disturbances begin during embryonic life. The syndrome has repeatedly been *seen in several members of the same* family, frequently accompanied by other congenital malformations, such as *spina bifida, harelip, or atresia of the* anus. Some authors claim that it is most frequent among Jewish and Spanish *people; mild degrees of hirsutism* are very common among Mediterranean races.

PATHOGENESIS

The immediate cause of hypercorticoidism, that is, the underlying adrenal changes, have been discussed in the chapter on pathologic anatomy. In some instances, the adrenal hyperfunction is "idiopathic" or due to a suprarenal-cortical neoplasm, about whose origin we know as little as about that of any other true tumor. A pituitary adenoma (usually basophilic), may also be responsible for diffuse hyperplasia or adenomatosis of the cortex with secondary hypercorticoidism. In this case, our understanding merely stops one link higher in the chain of events, since we do not know the factors responsible for pituitary tumor formation

If it is true that nephrosclerosis and renal hypertension are primarily hypercorticoid conditions, their original causative factor would be the adaptive reaction, elicited by exposure to some non-specific damaging agent

In any event, the clinical symptoms and signs of the hypercorticoid syndromes are fully accounted for by the excess production of cortical steroids, a fact best illustrated by the curative effect of adrenalectomy. The virilization is presumably due to increased elaboration of adrenal testoids, the feminization to folliculoids, the diabe-

tes to gluco-corticoids and the hypertension to mineralo-corticoids. The existence of separate lipo-corticoids is not fully proven but if such exist, they could explain the fat deposition characteristic of the adrenogenital syndrome. As previously emphasized, most cortical steroids exhibit several biologic effects and hence, any one of these could cause several of the typical manifestations.

CLINICAL COURSE

State. — It is hardly possible to draw a characteristic picture of "typical." adrenogenital syndrome because the various types (see : Classification) differ so markedly from each other. The cardinal manifestations are, pseudohermaphroditic traits and, since the condition is much more frequent in women, these usually correspond to virilization.

In children, the development of heterosexual features, tends to be much more pronounced than in adults: it is usually accompanied by premature sexual and somatic development. There may be precocious uterine bleeding, abnormal or precocious libido with other signs of mental precocity, over-development of the musculature, breast development in boys (rare) and early precipitous growth in length, followed by premature closure of the epiphyses and subsequent dwarfism, not unlike that of achondroplasia (short extremities in comparison to length of trunk).

The condition is too rare in adult males to deserve a general description, but in adult females it is common and characterized by hirsutism, with beard and moustache growth, loss of scalp hair, deepening of the voice, atrophy of the breasts, amenorrhea, enlargement of the clitoris, and other signs of virilism.

In addition to sexual changes, hypertension, glycosuria and a great tendency to adiposity are very characteristic The peculiar striation of the thighs and abdomen is reminiscent of Cushing's disease. The fat deposition is often particularly striking in the upper half of the body and the face, but it may be very marked and in that case generalized. The characteristic, somewhat flushed, round "moon face," of patients suffering from adrenogenital syndrome, tends to render them somewhat similar to each other.

Metabolism. — The B M.R is usually normal In the Achard-Thiers syndrome, there is HYPERGLYCEMIA AND GLYCOSURIA, accompanied by a marked decrease in glucose tolerance. However, glycosuria is comparatively rare among patients suffering from adrenogenital syndrome.

One of the most common manifestations of this syndrome is adiposity, but the fundamental nature of the LIPID METABOLISM disturbance has not yet been fully clarified. Sometimes, there is hypercholesterolemia

Changes in ELECTROLYTE AND WATER METABOLISM rarely occur, but if present, are very characteristic. There may be hypokalemia, hypernatremia, hypochloremia and a rise in the CO_2-combining power of the blood.

Growth and Bone Structure. — Usually children suffering from adiposogenital syndrome, grow very rapidly, at first Frequently, however, there is premature ossification of the junction cartilages and this interferes with subsequent growth in length

Cardiovascular System. — Hypertension is not uncommon in cases of adrenogenital syndrome, although it is by no means a constant finding. It tends to be accompanied by plethora and cardiac enlargement Removal of the causative adrenal growth, restores the blood pressure to normal in many, though not in all, instances. Apparently, the pressure remains high, even in the absence of excess corticoids, if the anatomic cardiovascular changes have progressed too far.

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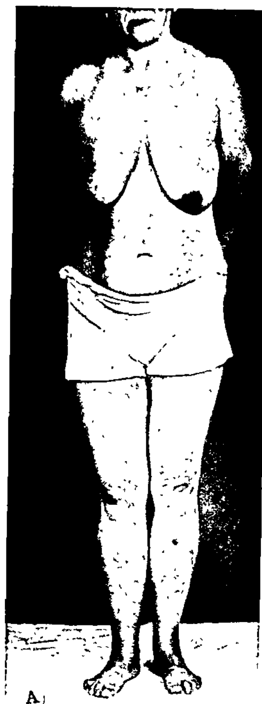
— B Marked apical baldness and masculine facies (Hirsutism of face not evident because of repeated electrolysis) (Cont'd)

Respiratory Organs. — Deepening of the voice is a very characteristic sign of the *adrenogenital syndrome*, especially in females. It is evident, not only in children, whose larynx is still in the process of growing, but, to a lesser extent, also in adult women. It is due to an actual anatomic transformation of the larynx from the female into the male type and rarely shows considerable improvement following ablation of the causative adrenal growth.

Muscles. — Muscular development and strength are often excessive in patients with the adrenogenital syndrome. This is particularly striking in women and children. The designation "enfants hercules" is often used to describe such children.

Nervous System. — Corresponding to the *somatic development*, precocious or homosexual libido and narcissism are frequently seen, although in some patients the mentality is not involved. When the sexual impulses become pathologic, due to an adrenal tumor, ablation of the latter may normalize the psyche. Women who merely lose their feminine libido, as a result of hypercorticoidism, may regain it after ablation of the growth and may subsequently even become pregnant Usually, however, such refeminization is incomplete or absent if the derangement is of long duration

Curiously, with the adrenogenital syndrome, homosexual tendencies are almost exclusively seen in women. Since in these, the development of the clitoris is particularly prominent, it is perhaps justified to consider the possibility that this somatic change, rather than a direct effect upon *nervous* centers, is responsible for the homosexual tendencies. The excessively developed, and highly sensitive, clitoris of these patients is constantly exposed to stimulation by rubbing against clothing or incidental touching, and the women soon learn that more intense



Adrenal virilism. — A. 45 year-old woman with amenorrhea, hirsutism and obesity of about twenty years duration Note large nipples and imprints from clothing (Cont'd)
(Courtesy of Dr E -J Kepler)



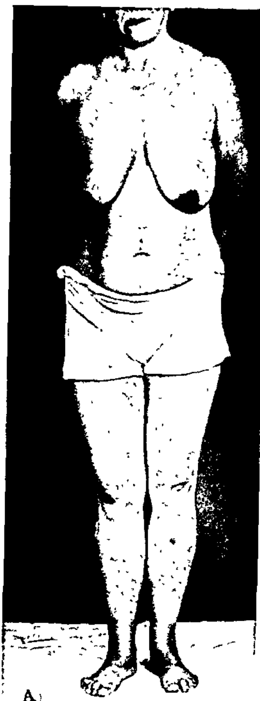
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(Courtesy of Dr. E.-J. Kepler)







"Feminizing" Adrenal-Cortical Carcinoma — A. Man, age 44 years, with carcinoma of the left suprarenal cortex and distinct gynecomastia There was impotence and complete disappearance of libido. The breasts consisted of fibrous tissue, with scattered glands The excretion of testoids and especially of folliculoids (up to several thousand M U /day) in the urine was increased. It is doubtful whether one should speak of "feminization" in such cases [illegible]

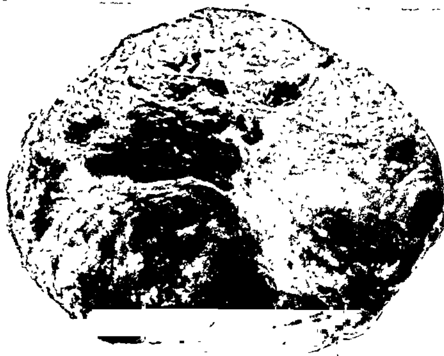
[illegible] Testis) — B. Atrophic testis with almost completely hyalinized tubules and nearly complete absence of Leydig cells — C. Part of the adrenal carcinoma showing marked polymorphism of cellular elements. In the center are groups of large cells with hyperchromatic nuclei

(Courtesy of Drs K Robalm and G Teilum)

both in primary and in secondary (hypophysogenic) cortical hyperfunction, indeed they disappear after ablation of the causative cortical neoplasm.

Urinary System. — Enlargement of the kidneys, sometimes with signs of nephrosclerosis, are mentioned in many autopsy reports of patients with adrenogenital syndrome However, the possible relationship between cortical hyperfunction and nephrosclerosis has only recently been recognized and hence most pathologists paid no special attention to the condition of the kidneys.

Renal calculi are common in patients who develop osteoporosis as a result of hypercorticoidism.



— C. Macroscopic aspect of adrenal tumor which was successfully removed Menses recurred three months after operation and became regular

orgasm is obtained by the stimulation of this organ, than of their usually hypoplastic vagina. Thus, the patient gradually comes to seek means of satisfying her desire by using the clitoris as a penis, even without there being any fundamental change in her female libido.

The intellectual development of children with adrenogenital syndrome is rarely precocious but they tend to be very immodest and aggressive. The pertinent patients I have seen were all strikingly unattractive, arrogant brats. They present difficult social problems because they have the sexual urge of the adult without the adults' inhibitions.

Skin. — HIRSUTISM is one of the most characteristic signs; in very mild cases, it may be the only obvious manifestation of the disease. Growth of hair on the upper lip and chin, temporal or apical baldness, as well as the typically male pubic hair line, are manifestations of virilism characteristic of the adrenogenital syndrome in women. In both sexes, there is also a great tendency to a particularly luxurious development of pubic and axillary hair and of hair on the thighs, calves and chest.

Follicular HYPERCERATOSIS, COMEDOS and ACNE are likewise common in such patients Sometimes there is MELANODERMA, reminiscent of Addison's disease This may be either generalized or patchy; it is not due to secondary destruction of the adrenals, since it can appear even in patients in whom only one adrenal is affected.

There was some controversy concerning the occurrence of CUTANEOUS STRIAE in the pure adrenogenital syndrome, due to a primary cortical tumor. Some investigators believed that these striations were characteristic of Cushing's disease with secondary adrenal involvement and represented a differential diagnostic criterion between this and the primarily adrenogenic hypercorticoidism It has been definitely shown, however, that they can occur



Adrenal carcinoma.

A and B 25-year-old woman with adrenal carcinoma of long standing which caused hirsutism, atrophy of the breasts, acne, purple striations, hypertension and finally death, due to metastases to the lungs Note dropping eyelids and mouth, as well as characteristic short greasy hair, with recession of the hairline at the temples

(After E -G Kepler and E -H Rynearson M Clin North America 24 1035 1940)

Sex Organs.— In FEMALE children the precocious, and usually abnormal, development of the sex organs is a characteristic and constant sign of the adrenogenital syndrome. The *vulva* is greatly enlarged, pubic hair appears very early (frequently showing the male type of distribution), and the *clitoris* is greatly hypertrophied often resembling a hypospadic penis. The female *prostate* and *seminal vesicles* may be well developed, sometimes communicating with the urethra through ejaculatory ducts Hence, actual ejaculation is possible, although, of course, the seminal fluid contains no spermatozoa, since these pseudohermaphrodites do not possess testes. If the condition develops very early during embryonic life, the vagina may be extremely hypoplastic and the labia majora tend to unite, more or less completely, in the mid-line, under the clitoris, so that the genital organs become very similar to those of the male. In fact some of these patients can be mistaken for boys with hypospadias and undescended testes. Provided there is no tumor, it may be best not to operate, and to bring these children up as "males," since after successful surgery they lose their masculine characteristics, without showing any definite female differentiation and hence become even more ambisexual.

Several cases are known in which *uterine bleeding* occurred in children less than four years of age. There are no adequate histologic studies of the accompanying endometrial changes but it appears unlikely that these bleedings represent true menstruation, since the ovaries do not mature precociously and ovulation or corpus luteum formation does not occur in the adrenogenital syndrome of children Yet, there is the possibility of luteoid formation by the adrenal cortex

The *mammary glands* may develop precociously in children but their development, like the precocious uterine hemorrhages, may cease at a later stage, when the heterosexual differentiation becomes more evident.



(For legend see p 173)



Adrenal carcinoma.

A and B, 25-year-old woman with adrenal carcinoma of long standing which caused hirsutism atrophy of the breasts acne purple striations hypertension and finally death due to metastases to the lungs Note dropping eyelids and mouth as well as characteristic short greasy hair with recession of the hairline at the temples

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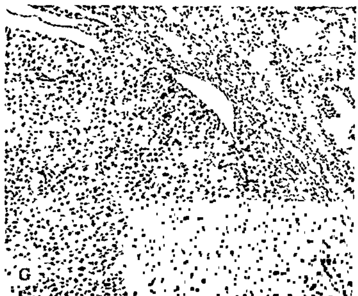
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(For legend see p 173)



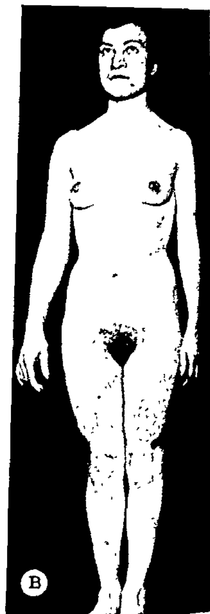


Metastasizing adrenal-cortical carcinoma. — A. and B. Preoperative appearance of woman, age 30 years, with virilizing adrenocortical carcinoma Abnormalities included amenorrhea,

— C. Enlar
moved —
huge, yello
mass at sit
F Several
G. Borderline between lung and

(Courtesy of Dr E.-P. McCullagh).


A


B


C


D

— E. *Hypertrophy of clitoris* *Removal of a cortical adenoma led to no significant improvement.*

Juvenile adrenogenital syndrome — A. and B [illegible]
[illegible] and 1½
4 months
[illegible] large and
[illegible] maturity
[illegible]hy. Breast
[illegible]vidence of
right flank
[illegible]onths post
operative: almost complete disappearance of pubic hair. Palpable breast tissue disappeared almost completely. Clitoris enlargement remains. (Same scale applies to C and D.) (Cont'd.)

(Courtesy of Dr. E. P. McCullagh)







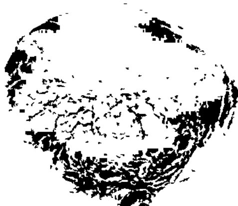


Adrenogenital syndrome. — **A.** Patient at 17 years of age when she was obese, but otherwise normal. — **B.** Patient at 23 years of age, beginning hirsutism under the chin. — **C.** Patient at 41 years of age. Hirsutism extends to mustache and there is loss of weight — **D.** Patient at 42 years of age, when hirsutism and loss of weight became aggravated About 6 years prior to this, she developed insulin-resistant diabetes, muscular atrophy and osteoporosis The urinary *17-KS is high* (20 mg /24 hrs) (Cont'd) (Courtesy of Dr A -B de Ulhôa Cintra)





Adrenogenital syndrome in a boy. — A. 11-month-old infant with adrenal-cortical tumor Note round 'moon-face', excessive hair growth on forehead and drooping of the angles of the mouth ('sun-fish mouth' in Kepler's terminology) — B Note stocky build and well-developed genitalia — C. Same boy ten months after removal of the adrenal tumor Note change in facies and body configuration as well as decrease in the size of the genitals The boy did not grow during this period — D Macroscopic view of the removed neoplasm
(Courtesy of Dr E J Kepler)


D



— E and F. Gross appearance of adrenal tumor.

A



— B. Same patient 2 years after removal of the adrenal tumor Note disappearance of acne and change in facies



Adrenal virilism. — A. Appearance of woman with cortical carcinoma and virilism prior to operation Note marked acne and roundish face (Cont d)
(Courtesy of Dr E J Kepler)



— B. Same patient 2 years after removal of the adrenal tumor. Note disappearance of acne and change in facies

In adults, the *ovaries* and *female accessory sex organs* (e.g., uterus, vagina, mammary gland) tend to be atrophic, and there is usually *amenorrhea*, probably as part of the pseudohermaphroditism.

In the MALE, the development of the sex organs show abnormalities which may be regarded as a counterpart, of what has just been said about the female. If the condition develops during early embryonic life, the *external* genitalia acquire a heterosexual character, so that one may easily mistake the atrophic and the hypospadic *penis* for a relatively large clitoris and vagina. In these very young pseudohermaphrodites, the *testes* are normal for the patient's age, but in adults they tend to be atrophic.

Excessive *mammary gland* development in *pseudohermaphroditic males* may sometimes be accompanied by actual lactation. In one such case, the enlarged mammary glands underwent rapid atrophy, following successful operation. It must be kept in mind, however, that testoids also cause mammary development and hence, breast growth in a male is not necessarily a true feminine characteristic, but may be merely due to excessive male hormone production.

COMPLICATIONS

Tumor METASTASES or adrenal hemorrhages, due to infiltrating cortical carcinomas may complicate the course of the adrenogenital syndrome. Fatal complications may also occur as a result of invasive growth into the adjacent kidney tissue.

An important "complication" of the adrenogenital syndrome in females is SUICIDE. The profound effect of heterosexual development upon the female *mentality* must not be underestimated. Even mere hirsutism may sufficiently disfigure the patient to cause serious disturbances in her mental equilibrium.

CARDIOVASCULAR COMPLICATIONS due to chronic *hypertension*, are comparatively rare in the adrenogenital syndrome. If renal hypertension of primarily adrenocortical origin should prove to be a common condition, the cardiovascular complications such as myocardial infarcts, cerebral hemorrhages, arteriosclerosis, periarteritis nodosa, etc., would assume importance.

DIAGNOSIS

The diagnosis of the adrenogenital syndrome is based upon:

(1) The *clinical manifestations* of the disease.

(2) Local signs of a lesion in the *adrenal region*.

(3) Detection of an excessive cortical hormone production, by bioassay or chemical analysis of *the urine*.

(4) Differential diagnostic *considerations*.

(1) The Clinical Manifestations of the Adrenogenital Syndrome. — In typical cases, the symptoms and signs, as described under "Clinical Course" are so characteristic that the diagnosis can be made, with a high degree of probability, without further investigation. Particularly valuable criteria are: the precocious and often heterosexual development in children and the pseudohermaphroditic traits in adults, especially if accompanied by hypertension, plethora and diabetes.

(2) Local Signs of a Lesion in the Adrenal region. — These are essentially the same as those described in connection with the diagnosis of Addison's disease, hence, we shall limit ourselves here to local signs particularly characteristic of hypercorticoidism as such.

Local manifestations in the adrenal region are most common in cases of adrenogenital syndrome due to cortical tumors. Here, a palpable or radio-





Aerograms of the adrenal. — A. Normal shadow of the adrenal — B Shadow of an enlarged adrenal (Courtesy of Drs M Malenchini E-B del Castillo and J. Roca)

logically demonstrable displacement of the kidney or an increased area of density, detectable by percussion, may be of diagnostic value. Indeed, especially after air injections, the adrenal tumor itself may be radiologically visible. Sometimes, the tumors are so large that they deform the lumbar region and compress adjacent nerves or vessels, thus eliciting lumbar pain and additional local signs. In doubtful cases an exploratory laparotomy may be necessary.

(3) Detection of an Excessive Cortical Hormone Production by Bioassay or Chemical Analysis of Urine or Blood. — An increased excretion of 17-KS (especially dehydro-iso-androsterone) as judged by chemical tests, or of TESTOIDS, as judged by bioassays, is frequently, though not always, demonstrable in the adrenogenital syndrome High 3(β)-hydroxy-17-KS are characteristic of cortical neoplasms, while normal levels usually, but not necessarily, exclude cortical tumors (See also The Steroids, The Testis.)

In a few instances, an increased urinary elimination of FOLLICULOIDS is noted in the adrenogenital syndrome, both in women and in men, irrespective of the presence or absence of "feminization."

The urinary elimination of PREGNANEDIOL, and other biologically INACTIVE STEROID DERIVATIVES, is frequently augmented in the adrenogenital syndrome, but further studies concerning the metabolism of the cortical hormones will be necessary before the significance of such tests can be properly evaluated Increased urinary excretion of LIFE-MAINTAINING CORTICOIDS, as judged by the cold resistance or glycogen deposition tests, is often very marked in hypercorticoidism of the Cushing syndrome type and may assume diagnostic significance.

(4) Differential Diagnostic Considerations. — Among the ovarian tumors the ARRHENOBLASTOMA may lead to virilism, similar to that seen in the adrenogenital syndrome. However, since this neoplasm consists of testicular elements, proliferating within the ovary, it causes a purer syndrome of virilization than the adrenal tumors and is unaccompanied by obesity, hypertension, striæ, osteoporosis and diabetes. In doubtful cases, pelvic or rectal exam-

ination, or even exploratory laparotomy, may be necessary to ascertain the diagnosis.

The so-called "OVARIAN HYPERNEPHROMA" is indistinguishable by its hormonal manifestations, from the adrenogenital syndrome of adrenal origin. This is not unexpected since both tumors actually consist of the same type of adrenal-cortical tissue, orthotopic in one case, ectopic in the other. Only local manifestations of a tumor in the ovarian region are of differential diagnostic significance.

LUTEOMAS AND LEYDIG CELL TUMORS OF THE OVARY are also very difficult to identify. The former may be indistinguishable from the hypernephroma of the ovary, even histologically The latter usually cause pure virilization, as does the arrhenoblastoma As these neoplasms are extraordinarily rare, they are not of great diagnostic importance

TRUE HERMAPHRODITISM is so rare that, for practical purposes, it hardly needs to be considered It is always congenital and reveals only sexual disturbances, without the metabolic and cardiovascular manifestations of the adrenogenital syndrome. Usually the accompanying malformations of the sex organs are much more severe than with adrenal tumors

TRUE OVARIAN PRECOCIOUS PUBERTY is also rare. It is characterized by a premature development of the ovary, with follicle maturation, ovulation and corpus luteum formation This is accompanied by more or less regular menstrual cycles and may result in pregnancy in girls as early as the eighth year of life.

FOLLICULOMAS, or persistent FOLLICLE CYSTS, tend to cause precocious "pseudopuberty" in infants. They are unaccompanied by precocious ovulation or the heterosexual, metabolic and cardiovascular manifestations of the hypercorticoid syndrome

TUMORS OF THE HYPOTHALAMUS and adjacent areas, often present diagnostic difficulties because they may elicit heterosexual characteristics, accompanied by hypertension (in this case, due to increased intracranial pressure). The differential diagnosis between this condition and the adrenogenital syndrome is hardly ever possible unless local signs reveal the site of the tumor; that is, increased intracranial pressure signs or radiologic evidence of an intracranial neoplasm in one case, signs of a tumor in the adrenal region in the other.

PINEAL TUMORS usually develop in children under 12 years of age and also tend to cause precocious sexual maturity. They have never been observed in females nor have they been found to elicit pseudohermaphroditism The somatic development is precocious but proportionate. The B.M.R. is frequently increased In early stages there may be generalized adiposity but later the patients become cachectic and local signs of intracranial pressure develop

CUSHING'S SYNDROME, resulting from a basophil adenoma of the anterior-lobe, (i e., Cushing's Disease), presents the most serious differential diagnostic difficulties. In fact, there are many cases which may be considered to be intermediate types between Cushing's syndrome and the adrenogenital syndrome, at least they have features of both, inasmuch as basophil anterior-lobe adenomas and adrenal-cortical adenomas develop simultaneously in the same patient In such instances, the entire symptomatology of the two syndromes is identical, except for the possible (rather rare) presence of local signs in the pituitary region (compression of the optic chiasma, increased intracranial pressure, radiologically detectable deformation of the sella) In characteristic cases of Cushing's disease, the increased red cell count, osteoporosis of the skull and spine and the metabolic manifestations tend to be

more prominent, while the sexual abnormalities are less conspicuous than in the adrenogenital syndrome. Yet there is no symptom or sign (not excluding the blood chemical changes) which could not occur in either malady with the possible exception of the clitoris enlargement; this apparently never occurs in Cushing's disease.

Certain THYMUS TUMORS may occur in conjunction with an otherwise typical Cushing's syndrome. In these, only local signs in the thymus region (dullness on percussion, X-ray shadow) permit the differential diagnosis.

PROGNOSIS

The prognosis of the adrenogenital syndrome depends largely on the causative adrenal lesions. In the case of simple hyperplasia, the course may extend over a whole lifetime, without causing any very serious disturbance. On the other hand, adenomas or carcinomas tend to progress.

Following early surgical ablation of adenomas or carcinomas, the prognosis is favorable if it is technically possible to remove all the tumor cells and if the patient survives the immediate shock of operation.

THERAPY

The indications for the SURGICAL TREATMENT of hypercorticoidism differ according to the nature of the underlying adrenal abnormality.

Malignant tumors of the adrenals should, of course, always be removed, whenever technically possible. Cortical carcinomas may cause great difficulties in this respect, owing to metastases or direct invasion into the renal vein, kidney and other adjacent tissues. Every effort should therefore be made to recognize malignant tumors, at an early stage, by surgical exploration of the adrenal region in all suspicious cases.

Heavy doses of cortical extract and desoxycorticosterone should be administered preventively several days before and after the operation, since the contralateral adrenal may be severely atrophic in the presence of a tumor in one gland. It is also important to explore the other adrenal, even if one gland has proven to be the bearer of the presumably causative tumor. In a few cases of adrenogenital syndrome there are bilateral, primary tumors, while in others, one adrenal may be completely destroyed by a growth which secondarily involves the other adrenal as well.

The prognosis of patients subjected to total bilateral adrenalectomy is extremely grave. Even if maximal doses of cortical extracts are administered, it is practically impossible to adjust the corticoid therapy to the varying requirements of everyday life. Very few patients have survived total bilateral adrenalectomy for more than a few weeks in spite of hormone therapy. Information, however, is limited almost entirely to the cases published by Huggins, who performed total adrenalectomy to alleviate cancer of the prostate.

Adrenal-cortical hyperplasia, with Cushing's syndrome, presents the problem of restoring the usually poor health of the patient. Reduction of the total mass of adrenal-cortical tissue by partial adrenalectomy (removal of one or partial resection of both glands), though logical, has rarely yielded very satisfactory results. Total bilateral adrenalectomy should not be tried until we learn more about substitution therapy.

Adrenal-cortical hyperplasia with postpuberally acquired pseudohermaphroditism does not tend to render the patient seriously ill and the external genitalia show only minor changes, such as enlargement of the clitoris. In these cases, extensive resection of adrenal tissue is usually inadvisable, because of the surgical risk and the probability of postoperative deterioration in the patient's health. Some in-

vestigators reported satisfactory results in similar instances, but usually the virilism (including hirsutism) tends to persist, although a transitory amelioration may occur.

Adrenal-cortical hyperplasia with prepuberally acquired pseudohermaphroditism, in its *mild forms*, is generally no indication for adrenal surgery, again because of the good health of these patients and the usually unsatisfactory correction of the virilism by partial adrenalectomy. In most pertinent cases, plastic surgical interventions, on the deformed external genitalia, give the most satisfactory results

In the more or less *complete forms* of this type of pseudohermaphroditism, *the patients develop into normal, vigorous "men,"* although legally and in the Catholic and Greek Orthodox Churches, they are regarded as women, if the female sex of the gonad is established by surgical exploration. Partial adrenalectomy or surgical attempts to make the external genitalia conform with the female sex of the gonads fail Both physically and psychologically, *these patients can make fairly normal "men," but invariably develop into very poor women* It must be remembered that these individuals are chemically and in most of their anatomic features, of the male sex. Plastic operations, psychotherapy and social arrangements facilitating their life as "men" are generally *most satisfactory to the patient.*

Hyperplasia of the adrenal cortex is frequently accompanied by the formation, usually multiple, of very benign adrenal adenomas. Since these have little or no tendency to undergo malignant transformation, they do not significantly alter the surgical indications as outlined above. On the other hand, if single, large adenomas are detected at exploratory laparotomy, they should be enucleated, as this is a simple operation and *such neoplasms often have a rapid growth rate and may become malignant.*

Among other possible therapeutic measures, the administration of FOLLICULOIDS may be mentioned, since *these have been reported to be beneficial* in some cases of virilism but their effect is usually very doubtful.

X-RAY TREATMENT of the hyperplastic adrenal may give beneficial results, but its value is so dubious that it cannot be recommended except for inoperable cases. Adrenal-cortical cancers are singularly resistant to X-rays.

The administration of high carbohydrate, low protein and low sodium DIETS, especially in combination with some acidifying salt such as ammonium chloride, would appear to be justified on the basis of experimental evidence (see . pages 122 and 126), since such *diets decrease corticoid hormone production* and antagonize the toxic effects of corticoids in animals. Up to the present, these dietary measures have not been subjected to adequate clinical trials.

As SYMPTOMATIC THERAPEUTIC MEASURES, electrolysis, *X-ray treatment* diathermia or depilatory *treatment of the hirsutism* may be recommended in otherwise incurable cases and in those not sufficiently severe to justify a surgical intervention

SPONTANEOUS HYPERCORTICOIDISM IN ANIMALS

Cases of pseudohermaphroditism, of presumably adrenal origin, have been noted for instance in the fowl. However, most cases of ambisexuality in animals are due to true bisexual development *of the gonads (true hermaphroditism)* or to ovarian and testicular tumors, while adrenal pseudohermaphroditism is extremely rare.

The spontaneous occurrence of adrenal tumors accompanied by cardiovascular lesions and periarteritis nodosa have also been described in animals.

HYPERADRENALINISM

(SYNONYMS: hyperepinephrinism, suprarenal sympathetic syndrome. — The terms, adrenal-medullary tumor, chromaffinoma, pheochromocytoma and paraganglioma of the adrenal are not truly synonymous with hyperadrenalinism. They merely designate the tumor itself, which usually elicits the syndrome.)

DEFINITION

Hyperadrenalinism is a condition in which the hormone production of the adrenal medulla is sufficiently increased *to produce detectable symptoms of* overdosage.

This disturbance is usually due to a benign adrenal-medullary tumor, developing from the chromaffin cells. Sometimes it may result from hyperplasia of the adrenal medulla and even from tumors or hyperplasia of the extra-adrenal, paraganglionic chromaffin tissue.

CLASSIFICATION

The only customary classification of hyperadrenalinism is according to the structure of the underlying ADRENAL LESION. Thus we distinguish:

(1) Benign pheochromocytomas
(2) Diffuse hyperplasia of the adrenal medulla.
(3) Malignant pheochromocytomas.
(4) Paragangliomas outside the adrenal

All but the first of these four types are great rarities.

INCIDENCE

Hyperadrenalinism is a rare disease, although many more cases have been observed than the approximately 150, which have been described in the literature. Among these, only very few were due to hyperplasia, medullary carcinomas or extra-adrenal paragangliomas

As far as one can tell from the small series of published cases, hyperadrenalinism occurs with about equal frequency in both sexes It can develop at any age, but is most common in middle-aged patients.

PATHOLOGIC ANATOMY

The morphologic characteristics of the underlying adrenal lesions will be discussed in the section on adrenal tumors and hence, need not be reconsidered here. (See p 191.)

PATHOGENESIS

Nothing is known about the primary cause of hyperadrenalinism. When it is due to a tumor, its etiology is as cryptic as that of other neoplasms; when it results from diffuse hyperplasia we know even less about its ultimate pathogenesis than about that of most other endocrine hyperplasias, since the adrenal medulla is not stimulated by any specific trophic hormone which could act as a causative agent. Theoretically, it is possible that chronic excitation of the secretory nerves could lead to functional hyperadrenalinism, but this, if it occurs, must be rare, since almost all published instances of this disease were due to demonstrable chromaffin tumors.

Except for the cause of the chromaffin-cell-stimulation the pathogenesis of the syndrome is readily understandable, since all the symptoms and signs are manifestly due to increased adrenaline production

That the spells often occur following exposure to diverse noxious agents, is not unexpected, since even the normal medullary cells discharge excess amounts of adrenaline in the first stage of the "alarm reaction." The principle characteristic of hyperadrenalinism is that the stores of adrenaline, and the hormone-producing ability of the

chromaffin cells, are very high, so that the normal emergency hyperadrenalinemia is greatly exaggerated.

CLINICAL COURSE

State. — The clinical picture of hyperadrenalinism of endogenous origin, is practically identical with that of exogenous adrenaline intoxication. There are paroxysmal spells of extreme hypertension, severe cardiac palpitation, emotional disturbances, sweating, nausea, headaches, abdominal pain, mydriasis, intense pallor, hyperglycemia with glycosuria and, sometimes, lung edema. It is particularly characteristic that even if the condition is relatively mild, severe paroxysms are readily elicited by any physical or psychic stress likely to cause adrenaline liberation. Even mere palpation of the abdomen or straining to empty the bladder and especially histamine or insulin injections can induce severe spells

Metabolism. — Spells of HYPERTHERMIA are frequent during the paroxysms of hyperadrenalinism. In one patient, the practically normal basal temperature rose to 107° F. as a result of excitement This rise in body temperature is accompanied by a corresponding increase in the B M.R.

Other important and frequent signs of this disease, are GLYCOSURIA, HYPERGLYCEMIA and mild ALBUMINURIA. The latter may be due to vascular disturbances within the kidney

Blood Picture. — There may be some erythrocytosis but this is inconstant.

Cardiovascular System. — Spells of HYPERTENSION are among the most constant clinical manifestations of hyperadrenalinism. They are usually transitory and appear in combination with other symptoms of adrenaline intoxication, such as pallor, hyperthermia, faintness, lung edema, mydriasis, etc. Occasionally, however, a more permanent increase in blood pressure is observed, which sometimes is as high as 260 to 300 mm. of mercury (systolic). In these cases there is often hypertensive retinitis. The B.M.R remains permanently very high (up to +70 to +100%), while spells no longer occur.

The pallor is due to the sudden constriction of the minute cutaneous BLOOD VESSELS, readily demonstrable with the capillaroscope. Generalized arteriosclerosis has been observed in several cases; this is particularly striking in children who otherwise rarely show any such vascular lesions. The phenomenon is apparently the clinical counterpart of the adrenaline sclerosis produced in animals by continuous overdosage with the hormone.

Hypertrophy of the HEART is an almost constant finding and probably a result of the hypertension. The pulse rate increases rapidly during the spells, just as it does following exogenous adrenaline administration. In a few cases, however, marked bradycardia has been noted during the attack This is understandable since adrenaline may also elicit either tachycardia or bradycardia, according to dosage and the responsiveness of the individual These changes in cardiac rhythm frequently elicit painful sensations and palpitation in the chest

Respiratory Organs. — Acute, hemorrhagic LUNG EDEMA is a very characteristic sign of experimental adrenaline intoxication and is also encountered during the spells of spontaneous hyperadrenalinism. It is frequently the immediate cause of death The lung edema may be so profuse that blood-stained foam fills the trachea and mouth and the patient actually suffocates in his own lung edema fluid

A marked increase in the RATE OF RESPIRATION is frequently noted during the spells, even in the absence of lung edema.

Other Changes. — Among other manifestations of hyperadrenalinism, multiple small HEMORRHAGES into the mucosa of the gastrointestinal tract, the liver and the kidneys are worthy of mention. PIGMENTATION OF THE SKIN is rare, although it has been observed occasionally, especially in the (comparatively common instances) in which hyperadrenalinism is combined with NEUROFIBROMATOSIS. Great EMOTIONAL INSTABILITY or profuse SWEATING has also been frequently noted during the attack and this may be accompanied by MYDRIASIS, excessive SALIVATION and ANURIA.

COMPLICATIONS

The complications of hyperadrenalinism usually occur during the spells. They consist of fatal lung edema, the rupture of a blood vessel or sudden death due to cardiac irregularities.

DIAGNOSIS

The very characteristic CLINICAL SYMPTOMATOLOGY of hyperadrenalinism renders it readily recognizable if the physician remembers to think of this rare disease as a possibility

In suspicious cases we must search for LOCAL SIGNS indicative of an adrenal tumor. The pertinent diagnostic technics are discussed in the chapter on Addison's disease. It is especially important to establish the side on which the tumor is located, in order to decide upon a correct surgical approach. Great care should be taken not to precipitate a fatal adrenaline discharge during the palpation of the adrenal region. It is true that a mild adrenaline discharge, thus produced, may help the diagnosis by provoking a spell, but this is a rather dangerous procedure.

The DIFFERENTIAL DIAGNOSIS must first consider the possibility of other adrenal tumors. Those of the cortex are almost invariably accompanied by sexual disturbances which are absent in hyperadrenalinism, other adrenal blastomas (e g., ganglioneuromas, sarcomas) do not give rise to any clinical manifestations of a hormonal disturbance, unless they destroy both adrenals and produce addisonism. Since even malignant tumors of the chromaffin tissue itself rarely, if ever, give rise to hyperadrenalinism, the identification of the syndrome practically limits the diagnosis to benign chromaffinomas and the (exceptional) diffuse hyperplasia of the medulla.

Other conditions, conducive to spells of hypertension, such as eclampsia, lead poisoning, certain infections, cranial traumatisms, etc., also have to be considered in formulating the definite diagnosis. In doubtful cases the precipitation of an adrenaline discharge by histamine injection may aid the diagnosis, but this is dangerous. Some ascribe diagnostic importance to the possibility of inhibiting the spells with sympatholytics (e.g., benzodioxanes).

PROGNOSIS

The speed, with which the disease develops, is extremely variable but spontaneous cures hardly ever occur. In the case of surgical therapy, performed with the precautions recommended in the following chapter, the prognosis is favorable. If the tumor is completely removed recurrences do not occur, since the causative neoplasms are almost invariably benign. In the absence of suitable therapy, death usually ensues during one of the spells as a result of cardiac complications, fatal lung edema or a fatal hemorrhage.

THERAPY

The logical therapy of hyperadrenalinism is the SURGICAL REMOVAL of the excessive medullary tissue. This has to be performed with extraordinary care because of the great shock-sensitivity of these patients. It is well to keep in mind that adrenal chromaffinomas may contain several thousand

times the lethal dose of the hormone and a sudden discharge of even a small percentage of this, may cause death. (See: Adrenaline Content of the Adrenals, on page 127.)

It is best not to tell the patient exactly when the operation will be performed and to pretreat with sedatives, so as to avoid any emotional upset. It is *imperative to handle the adrenals* as little as possible and to ligate their larger vessels before removing the gland, to avoid the sudden outflow of stored adrenaline. Most patients, who succumbed after the operation, did so as a result of the direct adrenaline overdosage precipitated by the operative intervention. Indeed, the sensitivity of the patients is so great that in many cases, death (usually from lung edema) ensued after minor incidental surgical interventions for other reasons, such as spinal anesthesia, the removal of hemorrhoids, extraction of a tooth or a normal delivery.

X-RAY TREATMENT has been attempted in several cases but is hardly justified unless the patient refuses operation There is a great danger of provoking fatal adrenaline liberation by the breakdown of the tumor; in the few patients who benefited from X-ray therapy, the improvement was usually only transient.

TUMORS OF THE ADRENALS

DEFINITION

With the adrenals, as in the case of several other endocrine glands, the distinction between hyperplasia and true tumor formation is somewhat artificial because of the many transitional types.

The classical cortical and medullary adenomas and carcinomas, conducive to hyperadrenalism, are discussed in conjunction with the resulting clinical syndromes in the chapters on hyperadrenalinism and hypercorticoidism, respectively. In this section we shall only attempt a purely morphologic characterization of the adrenal neoplasms.

CLASSIFICATION

The tumors of the adrenals may be classified as follows

(A) TUMORS OF THE ADRENAL CORTEX
- (1) Adenomas.
- (2) Carcinomas

(B) TUMORS OF THE ADRENAL MEDULLA.
- (1) Chromaffin tumors.
- (2) Neuroblastomas
- (3) Ganglioneuromas.

(C) TUMORS OF THE ADRENAL STROMA.
- (1) Sarcomas.
- (2) Lipomas.
- (3) Hemangiomas
- (4) Lymphangiomas

(D) SECONDARY (OR METASTATIC) TUMORS OF THE ADRENALS.

PATHOLOGIC ANATOMY

(A) TUMORS OF THE ADRENAL CORTEX — Presumably, most of the cortical cell tumors originate as adenomas but some of them subsequently become malignant.

(1) SMALL ADENOMAS OF THE ADRENAL CORTEX are so common that it is questionable whether they should be considered as pathologic. It is estimated that one out of every three adults has at least some evidence of cortical adenoma formation. Usually these neoplasms are only a few mm in diameter and are localized in the outer layer of the cortex Multiple, minute adenomas are indistinguishable from the so-called "nodular hyperplasia" of the cortex. They rarely produce any manifestations of hypercorticoidism unless they reach a considerable size

and large adenomas are rare. (See p. 163.)

(2) Carcinomas of the Adrenal Cortex are usually devoid of lipid and glycogen. They consist of cells having a distinctly epithelial character, which form strands and bands (like the fasciculata), or acini (like the glomerulosa). Sometimes the cells are arranged more or less irregularly around blood vessels in a "perithelioma-like" fashion. Often the tumors contain many giant cells and bear no resemblance to normal cortical tissue.

Macroscopically, these tumors are grey or greyish-yellow, soft and prone to hemorrhage. They are very malignant and tend to metastasize early, both through lymphatic and blood vessels into lymph nodes, liver, lung, brain and the contralateral adrenal. They often spread into the kidney, frequently through the adrenal and renal veins.

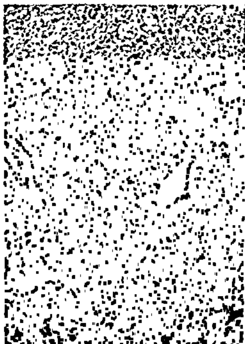
These neoplasms should be distinguished from the so-called "*Grawitz tumors,*" often referred to as "*hypernephromas of the kidney.*" The latter are light-yellowish, lipid-containing neoplasms situated within the kidney tissue. Their vacuolized cells bear a striking resemblance to those of the normal adrenal cortex, hence, their discoverer, Grawitz, thought they were adrenal-cortical carcinomas originating from embryologically misplaced cortical primordia, within the kidney tissue. A Grawitz tumor often contains papillae which resemble renal papillomas. It has a marked tendency to invade the kidney veins but causes no hypercorticoidism.

Since the term hypernephroma has been used indiscriminately to designate both renal carcinomas and the cancers of the adrenal cortex, it is preferable to dispense with this designation and to refer to the former as Grawitz tumors and to the latter as adrenal-cortical carcinomas. (See also p 163.)

(B) Tumors of the Adrenal Medulla. — These develop from endocrine or nervous elements.

(1) The chromaffin tumors (paragangliomas, chromaffinomas, pheochromocytomas) are rare, benign, epithelial neoplasms (adenomas), characterized by numerous cytoplasmic chromaffin granules. Their cells resemble those of the normal adrenal medulla and they are usually conducive to hyperadrenalinism (see: Hyperadrenalinism). Sometimes they remain asymptomatic and are found accidentally at autopsy.

The name "paraganglioma" has been given to these tumors because they occur, not only in the medulla of the adrenals, but also in extra-adrenal chromaffin tissue such as abdominal paraganglia, Zuckerkandl's organ or the carotid body. Frequently they contain follicle-like formations filled with cell debris and colloid ("struma



Pheochromocytoma. Benign pheochromocytoma which gave rise to typical signs of hyperadrenalinism Note the uniform, mature aspect of the cells (Low magnification)
(Courtesy of Dr P Masson)

times the lethal dose of the hormone and a sudden discharge of even a small percentage of this, may cause death. (See : Adrenaline Content of the Adrenals, on page 127.)

It is best not to tell the patient exactly when the operation will be performed and to pretreat with sedatives, so as to avoid any emotional upset. It is imperative to handle the adrenals as little as possible and to ligate their larger vessels before removing the gland, to avoid the sudden outflow of stored adrenaline. Most patients, who succumbed after the operation, did so as a result of the direct adrenaline overdosage precipitated by the operative intervention. Indeed, the sensitivity of the patients is so great that in many cases, death (usually from lung edema) ensued after minor incidental surgical interventions for other reasons, such as spinal anesthesia, the removal of hemorrhoids, extraction of a tooth or a normal delivery.

X-RAY TREATMENT has been attempted in several cases but is hardly justified unless the patient refuses operation. There is a great danger of provoking fatal adrenaline liberation by the breakdown of the tumor; in the few patients who benefited from X-ray therapy, the improvement was usually only transient.

TUMORS OF THE ADRENALS

DEFINITION

With the adrenals, as in the case of several other endocrine glands, the distinction between hyperplasia and true tumor formation is somewhat artificial because of the many transitional types.

The classical cortical and medullary adenomas and carcinomas, conducive to hyperadrenalism, are discussed in conjunction with the resulting clinical syndromes in the chapters on hyperadrenalinism and hypercorticoidism, respectively. In this section we shall only attempt a purely morphologic characterization of the adrenal neoplasms.

CLASSIFICATION

The tumors of the adrenals may be classified as follows

(A) TUMORS OF THE ADRENAL CORTEX
- (1) Adenomas
- (2) Carcinomas

(B) TUMORS OF THE ADRENAL MEDULLA
- (1) Chromaffin tumors.
- (2) Neuroblastomas.
- (3) Ganglioneuromas

(C) TUMORS OF THE ADRENAL STROMA.
- (1) Sarcomas.
- (2) Lipomas.
- (3) Hemangiomas.
- (4) Lymphangiomas.

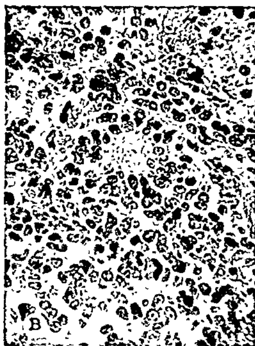
(D) SECONDARY (OR METASTATIC) TUMORS OF THE ADRENALS

PATHOLOGIC ANATOMY

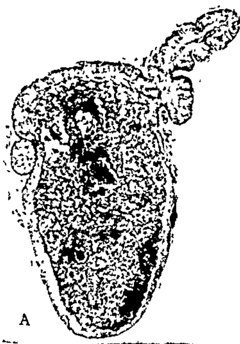
(A) TUMORS OF THE ADRENAL CORTEX —Presumably, most of the cortical cell tumors originate as adenomas but some of them subsequently become malignant.

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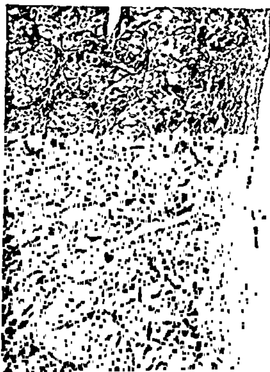
Neuroblastoma of adrenal. — A. Typical small cellular neuroblastoma of adrenal medulla Note rosettes (with light centers) The neoplasm is entirely limited to the medulla, the surrounding cortex is intact — B One of the "rosettes under high power.





Neuroblastoma of the adrenals — A Neuroblastoma of adrenal medulla surrounded by well-preserved, normal cortex (Very low magn) — B. Small, dark cells of very undifferentiated embryonic neuroblastoma are clearly separated by a thick connective tissue membrane from the larger, light cells of the adrenal cortex (Medium magn)

Pheochromocytoma. Benign pheochromocytoma which gave rise to typical signs of hyperadrenalinism Note the rather polymorph appearance of the cells which are much more atypical than in the tumor shown in previous figure. — A. low, and — B. high magnification. Note thick capsule separating tumor from normal cortex. (Courtesy of Dr P Masson)



Pheochromocytoma of the adrenal. Large cellular pheochromocytoma of the adrenal medulla Patient suffered from hyperadrenalinism.

of the suprarenal medulla"). Usually the cells are arranged in the form of trabeculae and solid cell-nests without follicle formation.

Chromaffin tumors of the adrenals are frequently found in patients suffering from v Recklinghausen's neurofibromatosis This led to the statement that this neoplasm is "a naevus of the sympathetic nervous system."

(2) Neuroblastomas (neuroblastoma sympathicum embryonale, immature neurocytoma, sympathogonioma, *sympathoblastoma)* are more immature types of medullary neoplasms, usually found in children or fetuses, hardly ever in adults. Since both the chromaffin cells and the sympathetic ganglion cells develop from the same embryonic sympathogonia, it is understandable that, depending upon the stage of their maturity, the tumors of the medulla may either develop into *chromaffin tumors* or consist of the less differentiated sympathogonia and sym-

they are essentially similar to neoplasms developing from nervous primordia in other organs. Ganglioneuromas may occur at any age.

(C) TUMORS OF THE ADRENAL STROMA. — SARCOMAS of the adrenals are extremely rare and probably most of the so-called round-cell and lymphosarcomas of the old literature were actually immature types of neuroblastomas (see above).

Much has been written about the usually bilateral MELANOSARCOMAS of the adrenals, but it is difficult to prove whether these actually originated in the suprarenals. In many carefully investigated cases, minute extra-adrenal primary melanosarcomas were found in other organs (e.g., eye, a melanotic naevus).

LIPOMAS, LYMPHANGIOMAS and OTHER NEOPLASMS of the adrenals are rarities

(D) SECONDARY (METASTATIC) TUMORS OF THE ADRENALS. — It is a curious fact that carcinomas originating in other organs (especially the breast and lung), frequently metastasize into the adrenals and often form deposits simultaneously in both glands The metastatic adrenal carcinomas may be the immediate cause of death due to the hypocorticoidism which they produce.



Metastatic carcinoma of the adrenal. Note squamous cell carcinoma islet within adrenal-cortical tissue The cancerous tissue contains cornified "pearls".

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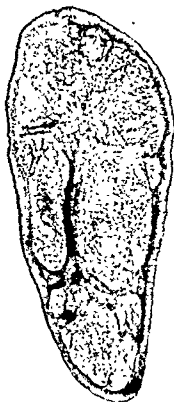
Reproduction of the two classical monographs of Thomas Addison, in which the disease, now bearing his name, was first described These writings, of one of the fathers of endocrinology, make most interesting and instructive reading, not only from a historic point of view, but also because they show how much can be accomplished, without any of the modern clinical and laboratory facilities, by keen observation of the living and dead patient They are prominent examples of concise and descriptive medical writing, as such, they are highly recommended to investigators, physicians and students alike

BROSTER, L. R. AND H W C VINES "*The Adrenal Cortex. A Surgical and Pathological Study*" London, H K. Lewis & Co Ltd (1933).

A monograph (94 pages, 4 colored illustrations, and 12 references), mainly concerned with the results of surgical therapy, and the interpretation of adrenal fuchsinophilia, in the adrenogenital syndrome

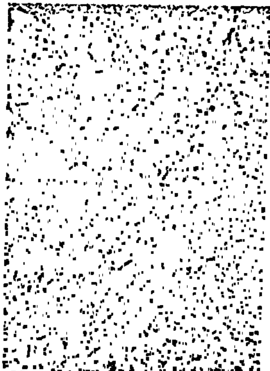
CAHILL, GEORGE F, MEYER M MELICOW AND H. H DARBY "*Adrenal cortical tumors The types of Nonhormonal and Hormonal Tumors*" Surgery, Gynecology and Obstetrics 74, 281 (1942)

A survey (25 pages, 30 illustrations, 74 references) of personal observations concerning patients with adrenal-cortical tumors Chief emphasis is laid upon the underlying histologic changes, the value of surgical therapy and diagnosis



pathoblasts (see: Embryology, on page 94). They have often been confused with round-cell or lympho-sarcomas. Their round cells are often arranged in rosettes surrounding indistinct fibrils. The neuroblastomas of the medulla are malignant metastasizing neoplasms similar to the corresponding tumors which originate from nervous elements in other regions.

(3) GANGLIONEUROMAS are much more mature, typical nerve-tissue neoplasms, consisting of a network of non-medullated nerve fibers, cells of Schwann's sheath and typical ganglion cells. The latter are often arranged in groups resembling ganglia. Ganglioneuromas are usually benign, hard, fibrillar, greyish tumors, found accidentally at autopsy in patients who have died of other diseases. Occasionally, however, they develop in the form of malignant, infiltrating and metastasizing neoplasms. Although these are primary tumors of the adrenals,





Ganglioneuroma of the adrenal medulla. — A. 4 year-old girl who died of rhabdomyosarcoma of the pelvis. The ganglioneuroma, limited to the adrenal medulla, was accidentally discovered at autopsy. — B. Higher magnification of cortico-medullary border zone (H & E) showing small cortical-cells (right) and large ganglion-cells of the tumor. — C. Section from the same region (Bielschovsky stain) to show fine nerve filaments (dark lines around ganglion cells).

(Courtesy of Dr P. Masson)

III

THE HYPOPHYSIS

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HISTORIC INTRODUCTION

The rôle of the pituitary was completely misunderstood by early physicians: indeed the name "pituitary" (from pituita=nasal mucus) was given to the gland by *Vesalius* (1543) in the erroneous belief that its function is to secrete fluid into the nose. Later, the anatomist *Willis* (1684) thought that the gland secreted cerebro-spinal fluid; conversely, *Magendie* (1847) assumed that the cerebro-spinal fluid is taken up by the gland and secreted into the blood.

It was the great merit of the French neurologist, *Pierre Marie* (1886), to recognize an interrelationship between the hypophysis and a type of GIGANTISM, "acromegaly." However, his interpretation was entirely erroneous. Having found that in acromegalic patients, the hypophysis is replaced by tumor tissue, he felt justified in concluding that the normal function of the gland is to inhibit somatic growth and that gigantism is a result of a lack of this inhibition due to destruction of the gland. This historic error clearly shows that even erroneous theories may be very valuable in directing investigations. Although Marie's assumption is exactly the opposite of the truth, yet he correctly recognized that the little gland, at the base of the brain, is a regulator of growth and should be investigated from this viewpoint.

Although the earlier literature contains many case reports of destructive hypophyseal lesions accompanied by DWARFISM and INFANTILISM, *Lorain* (1871) and *Erdheim* (1916) were the first to consider a causal relationship between pituitary damage and the inhibition of somatic development. The suspicion was raised that hypo- and not hyperpituitarism impedes growth Later *Simmonds* (1914) in Vienna, described a peculiar type of cachexia following pituitary disease in man This called attention to the metabolic functions of the gland.

Well-controlled experimental work was necessary, however, to clarify the intricate physiologic rôle played by the hypophysis There were some instructive early reports on the results of hypophysectomy in the dog (*Paulesco*, 1908; *Cushing et al.* 1910; *B. Aschner*, 1912, *Camus and Roussy*, 1913) and even the possibility of a substitution therapy had been established by experiments in lower vertebrates, such as tadpoles (*P. E Smith*, 1916, *B. M. Allen*, 1919). However, the function of the gland in mammals was very incompletely understood until 1921, when *H. M. Evans* conclusively proved that the anterior-lobe of the hypophysis contains a GROWTH-PROMOTING-HORMONE. This was demonstrated by injecting crushed bovine anterior-lobe tissue into rats, whose somatic growth was greatly stimulated by this procedure. Subsequently, it was shown that hypophysectomy inhibits somatic growth, as well as the development of the gonads, thyroids and adrenal cortex, and that hypophyseal extracts and implants restore all these changes to normal; indeed, they can even cause gigantism in hypophysectomized animals such as the rat (*P. E Smith*, 1930) This work culminated in the preparation of crystalline growth-hormone by *Li et al.* (1948).

DIETRICH, A. AND H. SIEGMUND: *"Die Nebenniere und das Chromaffine System (Paraganglien, Karotisdrüse, Steissdrüse)."* Henke und Lubarsch's Handbuch der speziellen Pathologischen Anatomie und Histologie. Drusen mit innerer Sekretion 8, 951 (1926).

This is one of the best sources of data concerning the pathologic anatomy of the adrenals and paraganglia (138 pages, 46 excellent illustrations, many of them in color, almost the entire pertinent literature up to about 1925). Highly recommended reading for all those interested in adrenal morphology. (In German)

GOLDZIEHER, MAX A *"The Adrenal Glands in Health and Disease."* F A. Davis Company Publ. Philadelphia (1944).

A treatise (727 pages, 81 illustrations, numerous references) surveying the morphology, physiology and diseases of the adrenal glands. The greatest emphasis is laid upon the clinical section.

HEARD, R. D. H: *Chemistry and Metabolism of the Adrenal Cortical Hormones* In The hormones Pincus, G and K.V. Thimann (Ed) Academic Press Inc., Publ, New York (1948)

An up-to-date review (80 pages, many tables and charts 271 references) compiled mainly from the chemist's point of view

KOHN, ALFRED *"Die Paraganglien"* Archiv fur mikroskopische Anatomie und Entwicklungsgeschiche 62, 263 (1903)

A monograph on the morphology of the paraganglia (102 pages, 27 illustrations, 74 references) by one of the best observers of these structures In spite of the date of this paper, it is highly recommended to those interested in this field (In German)

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Synopsis (7 pages, 3 illustrations, no references) of the main indications and surgical technics of adrenalectomy. (In French)

LOEB, ROBERT F *"Adrenal Insufficiency"* Bull New York Acad Med 16, 347 (1940)

A brief (20 pages, 9 illustrations, 31 references), but very authoritative summary of adrenal insufficiency from the clinician's point of view

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A monograph (346 pages, 2 drawings, 1118 references), mainly planned to act as a guide to literature on the experimental physiology of the adrenal cortex (In French)

ROWNTREE, LEONARD, G. AND A. M. SNELL. *"A clinical study of Addison's disease"* Mayo Clinic Monographs, W. B. Saunders Co., Philadelphia (1931).

An extensive, yet very readable, monograph, summarizing most of the important facts concerning Addison's disease, which were known up to the time of the discovery of active corticoid extracts

SILVER, SOLOMON *"The Cushing Syndrome, neoplasms of the adrenal gland"* Bull. New York Acad Med, 16, 368 (1940).

A stimulating graduate lecture (12 pages, 10 illustrations, 21 references) on personal observations concerning the clinical manifestations of Cushing's disease, with an attempt to elucidate their pathogenesis

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A monograph (304 pages, 42 excellent illustrations, some in color, numerous references) describing the morphology, physiology and diseases of the adrenal glands The main emphasis is laid upon clinical problems

SWINGLE, W. W AND J W REMINGTON. *"The Role of the Adrenal Cortex in Physiological Processes"* Physiological Reviews 24, 89 (1944)

A critical review (38 pages, no illustrations, 531 references) of the physiology of the adrenal cortex, written mainly as a guide to the pertinent modern literature

THADDEA, S *"Die Nebenniereninsuffizienz und ihr Formenkreis."* Stuttgart Ferdinand Enke (1941), Mit einem Geleitwort von G v Bergmann.

Monographic treatise (232 pages) of Addison's disease and associated syndromes (In German)

VACCAREZZA, AMERICO J *"Histofisiologie de la Corticosuprarrenal"* Medicina 5, 3 (1945)

Review (48 pages, 22 illustrations, 270 references) of the normal and pathologic histology of the adrenal cortex (In Spanish)

YOUNG, HUGH HAMPTON "Genital Abnormalities, Hermaphroditism Related Adrenal Diseases" The Williams & Wilkins Company, Baltimore (1937)

An excellent and detailed treatise (649 pages, 380 illustrations, numerous references) on hermaphroditism and pseudohermaphroditism This is perhaps the best contemporary monograph on the subject

endocrine tissue, nevertheless produces hormone-like substances. Subsequently in the United States, *Kamm* (1928) succeeded in separating the crude posterior-lobe extract (known as "pituitrin") into a VASOPRESSOR and an OXYTOCIC fraction. Later work suggested that the posteror-lobe also produces an ANTI-DIURETIC principle, the deficiency of which is probably the main factor responsible for diabetes insipidus. The relationship of this substance to the other two posterior-lobe hormones has still not been completely clarified, but it is probably identical with vasopressin.

In 1901, the Viennese physician, *Alfred Fröhlich*, described the ADIPOSO-GENITAL SYNDROME, which now bears his name. In this disease, deficient sexual development is combined with adiposity, due to hypothalamic lesions.

Recent investigations have brought forth increasingly more evidence that one of the most important physiologic rôles of the anterior-lobe is concerned with ADAPTATION to various types of non-specific stress and that many of the most common diseases of mankind (hypertension, nephrosclerosis, as well as certain cardiovascular and "rheumatic" diseases) may be "DISEASES OF ADAPTATION," due to a derangement of the pituitary response to stress. (See: General-Adaptation-Syndrome and the Diseases of Adaptation)

NORMAL MORPHOLOGY

ANATOMY

In man, the hypophysis cerebri (pituitary body, pituitary gland) is attached to the base of the brain by a thin stalk, emerging from the tuber cinereum The hypophysis is enclosed in the sella turcica or hypophyseal fossa of the sphenoid bone, which protects it on all sides and on its base. Its upper surface is covered by a circular fold of the dura mater, the diaphragma sellæ, which is perforated by the stalk. The subdural space does not extend around the pituitary body.

The gland consists of three main parts, namely:

(1) The ANTERIOR-LOBE (pars anterior, pars glandularis, anterior hypophysis), which consists of the *pars distalis* and continues anteriorly in the form of the *pars tuberalis*, a partly supra-diaphragmatic prolongation of the anterior-lobe attached to the stalk and tuber cinereum.

(2) The INTERMEDIATE-LOBE (pars intermedia), *which is absent or vestigial* in man but well developed in many animal species; it is sometimes regarded as part of the posterior-lobe although its structure is glandular.

(3) The POSTERIOR-LOBE (pars nervosa neurohypophysis, neural lobe).

The above nomenclature is currently employed in medical literature, but anatomists prefer the more elaborate one given in the table on p. 200.

The hypophysis measures about 1.2-1 5 cm. transversely, 1 0 cm. antero-posteriorly and 0 5 cm. vertically. It weighs about 0 5 to 0.6 gm. in the adult, being larger in women, especially in multiparæ, in whom it may exceed 1.0 gm

The anterior-lobe is pinkish-gray, the posterior-lobe is pearly gray and translucent, resembling nervous tissue. The anterior-lobe continues to grow until the 4th decade: after that it undergoes a gradual involution. The posterior-lobe is less likely to show changes in weight with progressing age

The PHARYNGEAL HYPOPHYSIS is a small vestigial remnant of Rathke's pouch which is often detectable between *the pharyngeal mucosa and the* sphenoid bone in man It resembles atrophic anterior-lobe tissue, but assumes importance only if it gives rise to tumor formation.

It is of historic interest that, in their earliest publications, *Evans and Long* (1921) came to the conclusion that while their anterior-hypophyseal extracts cause accelerated growth, "at the same time, the effect of the anterior-lobe has been to repress sexual development by delaying sexual maturity and lengthening the estrus cycles, in some cases estrus being entirely inhibited." Other investigators interpreted these findings as indicating that growth hormone inhibits sex development, especially since during the period of maximal growth in childhood, sexual development is dormant, while after cessation of growth, puberty ensues. *Evans and Long*, however, soon noted that while their experimental rats were almost continuously diestrous, the ovaries of these animals showed signs of excessive, abnormal luteinization and there was no parallelism between the degree of growth stimulation and the extent of luteinization. Hence, they correctly concluded that the gonadotrophic activity is probably independent of the growth hormone and we know now that the diestrus was merely due to the preponderance of luteinization over follicle stimulation, not to an actual inhibition of ovarian development.

The independent nature of the gonadotrophic activity soon received even more convincing support In 1926, *P. E Smith*, in America, and *B. Zondek*, in Germany, almost simultaneously observed that pituitary implants, introduced into sexually immature female rodents, produced precocious ovarian development, due to the presence of GONADOTROPHIN a sex-stimulating-principle of the anterior-lobe Subsequently, it was found that there are actually two *gonadotrophins*, one stimulating follicle maturation (FSH) and the other, luteinization of existing follicles (LH) Gonadotrophins had also been detected in large quantities in the urine of pregnant women; this was used in developing the Aschheim-Zondek test for pregnancy. They are also abundant in the placenta, probably because this organ is the source of the increased gonadotrophin production during gestation.

Experimental investigations of this type eventually led to the isolation of pure LUTEINIZING HORMONE or LH (*Li et al.* 1940), PROLACTIN OR LUTEOTROPHIN (*White et al. 1937*) and CORTICOTROPHIN (*Li et al.* 1942; *Sayers et al.* 1943). The FOLLICLE STIMULATING hormone or FSH, and THYROTROPHIN have not yet been isolated, but very pure preparations of them are available and their existence as separate hormonal principles is no longer in doubt.

All these observations centered interest upon the anterior-lobe of the hypophysis as an important hormone-producing organ and a regulator of the activity of other endocrine glands Probably several additional hormones are produced by the anterior-lobe and through them, it influences metabolism and the development of many organs However, the chemical identity of these latter hormones has not yet been fully clarified.

In 1932, *Harvey Cushing*, a surgeon of Boston, described the syndrome now known as CUSHING'S DISEASE, which is characterized by proliferation of the basophil cells in the anterior-lobe, adrenal-cortical hypertrophy, hypertension, as well as glycosuria and other metabolic disturbances. This discovery further emphasized the important action of the hypophysis upon metabolism.

Although many old case reports mentioned excessive diuresis in patients with pituitary disease, *E. Frank* (1912) was the first to clearly express the view that the hypophyseal lesion is probably the cause of the polyuria in DIABETES INSIPIDUS

In 1894, *Oliver and Schafer* in England, found that posterior-pituitary extracts exert a vasopressor action This suggested that the posterior-lobe, which, histologically, does not resemble

HISTOLOGY

Anterior-Lobe. — The anterior-lobe consists of epithelial cell nests and columns supported by a delicate connective tissue reticulum. Between the epithelial cells are wide sinusoids, whose walls contain sessile reticulo-endothelial macrophages. Only rarely do the epithelial cells form acinus-like structures, whose lumina include serous or colloid-like material, and which are reminiscent of thyroid follicles.

The epithelial cells of the anterior-lobe are of three main types :

(1) The ACIDOPHIL CELLS (oxyphil or alpha cells) represent about 37% of the total epithelial cell count and are characterized by numerous acidophilic granules within their cytoplasm. In some animal species they possess a characteristic Golgi net, which surrounds the nucleus like a cap.

(2) The BASOPHIL CELLS (beta cells) represent about 11% of the total cell count and are characterized by basophilic cytoplasmic granules. In certain animal species they possess a distinctive spherical Golgi net, which lies beside the nucleus. Although the Golgi apparatus itself is not visible without special stains, a "negative Golgi image" is often readily distinguishable on ordinary hematoxylin-eosin sections. In the basophil cells, this negative Golgi image is seen in the form of a pale ring-shaped hiatus in the cell body, with some cytoplasm in its center.

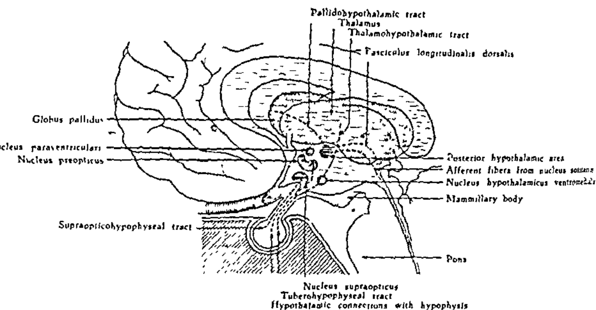
(3) The CHROMOPHOBE CELLS (chief cells, principal cells, reserve cells) represent the remaining approximately 50% of the epithelial cells in the anterior-lobe. They have no special affinity either to basic or acid dyes and hence, their comparatively scarce cytoplasm is pale on histologic sections. They are presumably the younger forms, the precursors of the basophilic and acidophilic cell types, respectively. Most of the chromophobe cells have a characteristic Golgi apparatus, corresponding either to the acidophilic or basophilic type.

Some workers distinguish a fourth cell type, the CARMINE CELL, which occurs in the anterior-lobe of certain species (e.g., dog, cat, rabbit). It has a special affinity for azo-carmine and erythrosin.

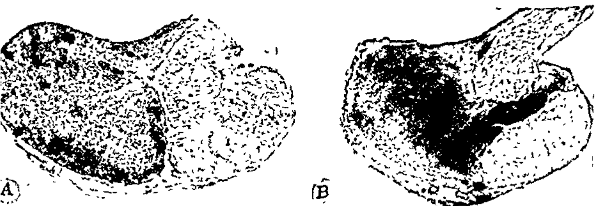
The Pars Tuberalis. — This is anatomically a prolongation of the anterior-lobe, which it resembles even histologically. Its cells do not contain chromophil granules however, but possess a rather diffusely basophilic cytoplasm. These cells may form irregular colloid-filled cavities, which generally appear only after birth. Scattered islets of squamous epithelial cells are also found in the pars tuberalis of man. They are vestigial rudiments of the embryonic buccal ectoderm from which the anterior-lobe is derived. Their chief importance lies in their tendency to give rise to tumor formation (craniopharyngiomas).

Intermediate-Lobe. — In man only a few, vestigial, cystic formations are found between the anterior- and posterior-lobes, but in most animals the intermediate-lobe is well developed, in the form of a more or less regular disc between the anterior- and posterior-hypophysis. Its cells contain no chromophil granules, but are rather diffusely basophilic. They are closely packed, with only a fine reticular stroma between them.

Posterior-Lobe. — In man, this part is composed almost entirely of irregular, usually spindle-shaped cells, with fine processes. It resembles the glia-containing portions of nervous tissue. However, the specific posterior-lobe cells or "PITUICYTES" are not modified nerve cells. They contain no Nissl substance and must be regarded as of ependymal origin. Numerous HYALINE BODIES (bodies of Herring) are seen between the fibers of the pars nervosa, especially near the floor of the third ventricle, under the ependyma. Their origin and function are not known. There are also many NERVE FIBERS in the posterior-



Schematic drawing illustrating interrelation between hypothalamic area and pituitary



Normal hypophysis (Man) — A. Very low magnification of a sagittal section through the pituitary Dark anterior-lobe, light posterior-lobe and barely visible cystlets corresponding to 'intermediate-lobe' between the two The pars tuberalis extends upwards from the anterior-lobe towards the hypothalamus — B. Another normal human hypophysis (courtesy of Dr W Bonin) in which stalk and 'intermediate-lobe cysts' are more evident

Terminology of the mammalian hypophysis recommended by the International Commission on Anatomic Nomenclature

	MAJOR DIVISIONS	SUBDIVISIONS	
ADENOHYPOPHYSIS	Lobus glandularis	1 Pars distalis 2 Pars tuberalis	Anterior-lobe
		3 Pars intermedia	Posterior-lobe
NEUROHYPOPHYSIS	Lobus Nervosus (neural lobe)	1 Processus infundibuli	Posterior-lobe
	Infundibulum (neural stalk)	1 Pediculus infundibularis (stem) 2 Bulbus infundibularis (bulb) 3 Labrum Infundibularis (rim) or median eminence of the tuber cinereum	

lobe; they come from the brain through the stalk.

BASOPHIL CELLS are almost invariably found in the pars nervosa of man. It is believed that these invade the tissue from the anterior- lobe and subsequently decompose.

The Stroma. — The stroma of the hypophysis consists of a delicate connective tissue network.

The gland receives the superior hypophyseal ARTERIES in the form of several branches, which arise from the internal carotid and posterior communicating arteries. These anastomose with each other, as well as with those of the opposite side, on the infundibulum and stalk. Arterial branches enter the stalk and break up into sinusoids within its substance. Other small arteries proceed directly to the anterior-lobe and split up into sinusoids there. The inferior hypophyseal arteries are two paired branches of the internal carotid, which pass through the cavernous sinus and, after anastomosing on the dorsal side of the gland, supply the pars tuberalis and the posterior-lobe.

In the hypophysis, we find both portal and systemic VEINS The portal veins come from the capillaries of the stalk and tuber region. After collecting into larger venules, they split up into a second capillary network within the hypo physis. Direct observation in amphibia proved that the blood flow in these portal veins is caudally directed, from the hypothalamus to the pars distalis. The systemic veins are represented by the lateral hypophyseal veins draining from the anterior-lobe and the infundibular process into the cavernous or intercavernous sinuses.

The physiologic importance of the portal circulation in the hypophysis is not yet understood but it is interesting to speculate upon the fact that all three organs which produce active pressor substances the adrenal medulla, the renal tubules and the posterior-hypophysis possess a purely or almost purely venous circulation Perhaps a low intravascular pressure or anaerobic conditions of metabolism are favorable for the production of pressor substances

A thick tract of unmyelinated NERVE fibers originates in the vicinity of the supra-optic nucleus, just above the optic chiasm, and descends through the stalk to the pars nervosa. A few fibers of the tract continue into the pars intermedia. Some of these have branched endings which may possess large end-bulbs. The anterior-lobe receives unmyelinated fibers from the paraventricular nuclei and the carotid plexus These terminate between the epithelial cells.

COMPARATIVE MORPHOLOGY

It is questionable whether there is any organ corresponding to the hypophysis in INVERTEBRATES, although the "X organ" in the eye-stalk of some crustaceans and the corpora cardiaca and allata of periplaneta have been suspected to be precursors of the pituitary.

In AMPHIOXUS, there is a glandular organ, corresponding to the anterior-lobe of the hypophysis, but no infundibulum.

In CYCLOSTOMATA, (e.g , petromyzon fluviatilis), the hypophysis is a flat organ attached to the base of the brain. It consists of an anterior-lobe, which contains epithelial tubules, a distinct intermediate-lobe and a thin posterior-lobe.

In HIGHER VERTEBRATES, the pituitary is always well developed and essentially of the same structure as in man. However, in some (fowl, armadillo, manatee, whale) *the intermediate-lobe is missing*, while in others the anterior- and posterior-lobes are almost entirely separate, there being only a cylindrical stalk-like connection between the two (e.g , whale) A remnant of the lumen of the originally hollow pars distalis primordium, the "residual lumen," persists throughout adult life between the anterior and intermediate-lobes in most animal species (rodents, cat, etc.) but not in man

It is interesting that although in man *there is a certain proportionality* between the weight of the pituitary and the size of the individual, such does not



Normal hypophysis (Man) — A Anterior-lobe showing islets of large eosinophils (dark) and basophile

lobe does not prevent the continued function of the posterior or middle-lobes, and vice versa.

Interrelations Between the Various Cell Types of the Anterior-lobe. — In the past it had been thought that basophils can be transformed into acidophils and vice versa, since certain investigators believed to have seen "TRANSITIONAL CELLS," containing both basophilic and acidophilic granules. It has been shown, however, that the supposedly acidophilic granules in basophils, were actually mitochondria and that true transitional types do not occur. When discussing the histology of the anterior-lobe, we mentioned that the Golgi apparatus has a different shape in the acidophils and basophils and that even among the chromophobes, some have one and some the other type of Golgi net. This led to the theory that the nature of a certain chromophobe cell is predetermined before granules develop in it, so that certain chromophobes can only develop into basophils others only into acidophils. If later chromophils lose their granules due to exhaustive incretion, they revert into chromophobes, which still retain their original, either eosinophilic or basophilic character, as regards the Golgi net (*Severinghaus*).

It has been claimed (*Collin*) that anterior-lobe cells may multiply by "ENDOCYTOGENESIS," that is, by the formation of a new cell within the cytoplasm of another. It has subsequently been demonstrated, however, that histologic pictures suggesting a cell within another cell are artefacts, due to the invagination of a small cell into the cytoplasm of a larger one. It is now generally agreed that the cells of the anterior-lobe, like those of other organs, multiply almost exclusively by mitotic and, to a negligible extent, by amitotic division.

Theories Concerning the Pathways of Secretion. — There has been much discussion concerning the pathways through which the hormones of the pituitary reach the target organs upon which they act. The fundamental basis of all morphologic studies concerning the pathways of hormone secretion is the assumption that the hormone precursors, or the hormones themselves, are visible in histologic sections. This has never been proven, but it is tacitly assumed by most morphologists that the tingible granules are hormone carriers, precursors, or (less likely) the hormones themselves, and hence, that by following the discharge of these granules from the cytoplasm we may gain knowledge concerning the mechanism of hormone secretion In the case of the adrenal medulla, there is good evidence indicating that the chromaffin granules are actually adrenaline or its precursor, but, in the case of the anterior-lobe, the hormonal nature of the tingible granules is much more hypothetic. It is assumed, however, that cells rich in granules, are storing their secretion, while degranulated cells have discharged it.

The simplest and probably best proven type of pituitary secretion is the DIRECT DISCHARGE OF HORMONES INTO THE BLOOD VESSELS, or "hemocriny" (*Collin*) as it occurs in other endocrine glands On histologic sections, granules similar to those seen in the cytoplasm of the anterior-lobe cells, can often be distinguished within the lumina of the sinusoids.

Allegedly there is another mode of secretion in the pituitary, the DIRECT DISCHARGE INTO THE HYPOTHALAMUS by way of the posterior-lobe and stalk. This process has been designated as "neurocriny" (*Collin*). On histologic sections, it is possible to detect colloid globules, which apparently come from the pars anterior and invade the posterior-lobe, subsequently ascending through the stalk into the hypothalamus The existence of such granules, the so-called "Herring bodies" has been established beyond doubt, but it is difficult to prove that they are derived from epithelial portions of the anterior

exist if we compare different species For instance, in certain whales (Balaenoptera Sibbaldii) weighing 100.000-150,000 Kg, the average weight of the anterior-lobe is only 32.5 gm., that of the posterior lobe 1.4 gm.

EMBRYOLOGY

The glandular portions of the hypophysis develop from an ectodermal pocket, originally located in front of the pharyngeal membrane. From here an invagination (Rathke's pouch) emerges in the form of a shallow sack in embryos about 3 mm. in length. It gradually comes into contact with a similar, glove-finger-like invagination of the infundibulum, which grows in the opposite direction and represents the primordium of the posterior-lobe. After the two primordia meet, Rathke's pouch loses its connections with the oral ectoderm at the end of the second month of embryonic development. The lumen of the pouch becomes the "residual lumen" of the adult gland. It persists during postnatal life in most animal species, although in man it is reduced to isolated cystic sacs.

The characteristic permanent structure of the hypophysis is attained at about the 3rd and 4th month, at which time the rostral wall of Rathke's pouch proliferates and differentiates into the ANTERIOR-LOBE *The portion between* the original lumen and the posterior-lobe remains less developed in all animal species It may involute or differentiate into the PARS INTERMEDIA The so-called "PARS TUBERALIS" stretches forward along the infundibulum and is eventually partly situated above the diaphragma sellæ. It is also a derivative of Rathke's pouch and essentially of the same origin as the anterior-lobe.

The POSTERIOR-LOBE likewise tends to lose its lumen, a prolongation of the third ventricle, although a small recess persists in man, and deep invaginations are retained during postnatal life in many animal species.

THEORIES CONCERNING THE HISTOPHYSIOLOGY OF THE HYPOPHYSIS

It is difficult to understand why three apparently independent endocrine glands, the three lobes of the hypophysis, are joined into a single organ and why they are placed into such intimate contact with the hypothalamic centers. Could it be that the hormones of one lobe are manufactured from precursors furnished by another? Is the special type of circulation in the pituitary a common prerequisite for the production of hormones by the several lobes? Does the anatomic union of the three parts — and their location in the particular position which they occupy — occur because of a common dependence upon direct nervous stimuli from the hypothalamic region? Could the three lobes secrete their products directly into the adjacent vegetative centers of the brain? All these are intriguing questions, but only some of them lend themselves to an analysis by the methods known to us at the present time

Interdependence of the Various Pituitary Cell Types and the Adjacent Brain Centers. — Transplants of pure anterior-lobe tissue take quite readily in hypophysectomized animals and continue to produce somatotrophic, thyrotrophic, gonadotrophic, adrenotrophic *and other hormones, as judged by the fact that the usual consequences of hypophysectomy are prevented by these grafts.* This does not mean that the endocrine functions of the anterior-lobe are independent of the other lobes or of direct nervous stimuli reaching it through the stalk It is quite possible that the hormone production of the transplants is not entirely normal, but we may conclude that, in principle, anterior-lobe cells are capable of continuing their hormone production when transposed into an abnormal location

Similarly, it may be said, on the basis of partial hypophysectomy experiments, that isolated removal of the anterior-

ciated with acromegaly. Furthermore, in some animals (e g., pigeon) eosinophils are especially plentiful in the anterior-lobe during the period of maximal growth, and in certain strains of dwarf mice, eosinophils are entirely absent from the hypophysis. Since these mice grow up to normal size if treated with implants of normal pituitaries, it was thought that the stunting of their growth results from the deficient development of the anterior-lobe eosinophils. It should be emphasized, however, that both the stunted growth and the absence of eosinophils are recessive hereditary characteristics and that the individuals in which these features are manifest, are sterile because of gonadal atrophy. The animals are not congenitally irresponsive to the pituitary hormones, since hypophyseal extracts restore both the growth-rate and the atrophic gonads. Hence it would appear that not only the somatotrophic but also the gonadotrophic activity is to some extent linked with the eosinophils.

GONADOTROPHINS are allegedly elaborated mainly by the basophils, since castration causes a pronounced increase in the gonadotrophin content of the anterior-lobe and urine (e g., man), simultaneously with a marked hypertrophy of the anterior-lobe basophils (e g., rat). Furthermore, cattle pituitary is practically free of gonadotrophic hormones, except along the borderline of the middle-lobe where basophils are plentiful On the other hand, extracts of both eosinophilic and basophilic adenomas of human pituitaries can cause precocious sexual maturity in rodents, and castration causes proliferation of eosinophils in the anterior-lobe of man and most animal species other than the rat It is not improbable, therefore, that the eosinophils also participate in gonadotrophin production. There is some evidence that the basophils produce FSH, the eosinophils LH

The CORTICOTROPHINS appear to be chiefly elaborated by the basophils, since in Cushing's disease, basophilic adenomas of the anterior-lobe are accompanied by proliferation of adreno-cortical tissue and an increased corticotrophin production.

It has been claimed that PROLACTIN is secreted chiefly by the basophils, since these reach a maximal development in pigeons when the crop gland is fully functional.

It must be admitted, however, that all this evidence concerning the probable origin of the various anterior-lobe hormones is far from convincing, and even less is known about the cell-type responsible for the elaboration of OTHER ANTERIOR-LOBE PRINCIPLES.

INTERMEDIN, the chromatophore dilating hormone, arises in the intermediate-lobe in those animal species in which such a structure is present. This is shown by experiments indicating that only extirpation of the intermediate-lobe causes deficiency, and implantation of intermediate-lobe tissue results in symptoms of overdosage with this hormone. However, it must be admitted that in man, in whom a distinct intermediate-lobe does not develop, intermedin is demonstrable in the anterior-lobe, and to a lesser extent in the posterior-lobe tissue. Perhaps, in man, other cell elements have taken over the functions of the intermediate-lobe.

The vasopressor and oxytocic POSTERIOR-LOBE HORMONES are apparently both elaborated by the pituicytes, since other potentially endocrine cells are not demonstrable in the pars nervosa. In any event, it is certain that some elements in the posterior-lobe, and perhaps also the adjacent hypothalamic region, are the source of these hormones, because the anterior and intermediate-lobes are virtually free of them, and anterior or intermediate-lobe removal causes no deficiency manifestation in this respect

or middle-lobe, which then enter into the nervous system. It has been pointed out that certain secreting neurons in the hypothalamic region, especially in the *supraoptic* and paraventricular nucleus of many vertebrates, are capable of *forming colloid* and apparently represent an endocrine structure, the "midbrain gland" (*Scharrer, 1932*). Consequently, the mere presence of colloid granules in these neurons does not necessarily prove that they come from the pituitary.

There is increasingly more evidence to show that posterior and intermediate-lobe hormones are present in considerable quantities within the tissue of the tuber cinereum. It has not been possible to demonstrate, however, whether these substances are formed locally or come from the hypophysis through the stalk. Anterior-lobe hormones are present only in traces in the nervous tissue adjacent to the anterior-pituitary.

On histologic sections we sometimes see the hyaline colloid bodies (supposedly derived from the pituitary) entering the cerebrospinal fluid through the ependyma of the third ventricle This has been interpreted as indicating a DIRECT SECRETION OF PITUITARY HORMONES INTO THE CEREBROSPINAL FLUID or "hydrencephalocriny" (*Collin*) While the existence of such histologic pictures is undeniable, it is difficult to interpret them. Vasopressor and oxytocic substances have been demonstrated in the cerebrospinal fluid of the third ventricle in sufficiently high concentrations to suggest (*Cushing and Goetsch, 1910*) that these principles are, at least partly, discharged directly into the cerebrospinal fluid. On the other hand, only insignificant traces of anterior-lobe hormones are found in the cerebrospinal fluid and hence, the latter are probably not discharged through the same mechanism

The discovery of the pituitary portal vein system led to the assumption of yet another secretory pathway, the SECRETION OF HORMONES INTO THE PITUITARY "PORTAL" CAPILLARIES, with subsequent migration through the portal veins to the hypothalamic centers, in which these vessels form a second capillary network. This has been termed "hemoneurocriny" (*Collin*). Recent investigations suggest, however, that the direction of the blood flow in the pituitary portal circulation is from the hypothalamus to the pituitary, so that if this vascular system were of importance in the direct transfer of hormones, the latter would have to originate in the hypothalamic region and act upon the pituitary, rather than vice versa.

Since complete transection of the pituitary stalk results in no pronounced deficiency symptoms, it appears that neurocrine, hydrencephalocrine, hemoneurocrine secretion, and even the direct nervous connections between the pituitary and the hypothalamus are not indispensable. Yet, if pituitary hormones acted directly upon vegetative centers, smaller concentrations would suffice if they reached the centers directly, than if they were diluted by the entire blood volume after entering the general circulation Furthermore, the nervous regulation of pituitary hormone production may aid in the accurate adjustment of endocrine secretion to functional needs In any case the anatomic continuity, between the pituitary and the adjacent vegetative centers, is indispensable for the function of the posterior-lobe

Which Cell Produces Which Hormone? — There are only three clearly distinguishable cell types in the anterior-lobe. We do not know how many hormones the pars distalis produces, but, since it certainly elaborates more than three clinically different principles, it is evident that several hormones must originate from the same cell type

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only five of which (the follicle-stimulating luteotrophic, somatotrophic, adrenocorticotrophic and luteinizing hormones) have been isolated in pure form. There is convincing evidence that the thyrotrophic activity of anterior-lobe extracts is likewise due to a separate hormone

Since the purification of these principles has only recently been accomplished, it has not yet been possible to examine to what extent they and their combinations can duplicate the manifold effects obtainable with impure anterior-lobe extracts The latter produce a variety of biologic effects, which may be due to their content in additional hormones which have hitherto not been isolated, however, they could also be due to one of the above-mentioned six authenticated hormones, or to combinations of the same

In a discussion of the anterior-lobe hormones it is well to keep in mind that, depending upon dosage, route of administration, simultaneous treatment with other substances, etc., the actions of a hormone can be most significantly modified, hence great care should be exercised before we postulate the existence of new principles

It may help orientation in this complex field to enumerate the AUTHENTICATED ANTERIOR-LOBE HORMONES, together with their abbreviated names (in brackets) and synonyms, as well as a few of their chief characteristics.

(1) FOLLICLE-STIMULATING HORMONE (FSH). Synonyms · follicle stimulator, thylakentrin. This substance has recently been isolated (*Li et al 1949*) in pure form as shown by electrophoresis, ultracentrifuge and diffusion studies Its isoelectric point is at pH 4 5 and its molecular weight is 60,000 Highly purified preparations are characterized by their ability to stimulate the growth of the granulosa cells in the ovaries of hypophysectomized animals, without preventing the atrophy of the theca cells and without eliciting folliculoid hormone secretion by the ovaries. The hormone also stimulates the seminiferous epithelium in the testes of intact or hypophysectomized animals. It is especially abundant in: the anterior-lobe, the urine of castrates, and pregnant mare serum (PMS).

(2) LUTEINIZING HORMONE (LH). *Synonyms* : interstitial-cell-stimulating-hormone (ICSH), chorionic gonadotrophin, metakentrin. It transforms mature ovarian follicles into corpora lutea and stimulates the growth and folliculoid hormone secretion of the theca cells, even in the hypophysectomized animal. It probably also enhances folliculoid secretion by the granulosa and corpus luteum, but does not prevent the atrophy of preëxisting corpora lutea, nor does it cause them to secrete luteoid hormones. It stimulates the development and testoid hormone secretion of the Leydig cells, both in intact and in hypophysectomized males It is particularly abundant in· anterior-lobe tissue, human placenta and human pregnancy urine (PU). Electrophoretically pure, crystalline human "chorionic gonadotrophin" has been prepared 6-8000 I.U./mg, causes ovulation in women (*Claisson et al. 1948*).

(3) LUTEOTROPHIC HORMONE (LTH). *Synonyms* : luteotrophin, mammotrophin, prolactin, galactin, lactogenic hormone The chief characteristics of this principle are that it maintains fully formed corpora lutea in the ovaries of intact or hypophysectomized animals and causes them to secrete luteoid hormone. It also stimulates milk secretion, but only if the mammary glands have previously been brought to full development. In the pigeon, it causes growth and secretion of the crop glands. It occurs in significant quantities only in anterior-lobe tissue.

The above-mentioned three hormones are collectively referred to as *gonadotrophins* or gonadotrophic hormones, since they are the chief regulators of gonadal activity.

(4) CORTICOTROPHIC HORMONES (ACTH). *Synonyms* : Adreno-corticotrophic hormone, adrenotrophin, corticotrophin, adrenotrophic hormone, corticotrophic hormone. This substance has been isolated in pure form. It stimulates the growth and hormone produc-

CHEMISTRY OF THE HYPOPHYSIS

CHEMICAL COMPOSITION OF THE GLAND

Since the chemistry of the various hypophyseal hormones will be discussed in the next chapter, it suffices here to give a brief account of the other chemical constituents which make up the tissue of the pituitary body.

The CARBOHYDRATE content of the hypophysis is low In cattle only about 1.5% (of the dry weight) of the anterior-lobe and 1.1% of the posterior-lobe, is extractable sugar.

The LIPID content of cattle pituitary has been estimated to be about 14% (of the dry weight) in the anterior, and 20% in the posterior-lobe tissue. The cholesterol content of the anterior-hypophysis (1.65%) is also lower than that of posterior-lobe (2.12%). It has been noted, in several species, that the lipid content of the pituitary tends to decrease during the breeding season.

The PROTEIN content of cattle anterior-lobe is about 78%, and that of the posterior-lobe 66% of the dry weight

Among the INORGANIC constituents of the hypophysis, the *iodine* content received special attention Dried cattle anterior-lobe powder has an iodine content of about 0.13-0 14 mg /gm The iodine content of one human pituitary is estimated to be about 13γ; it tends to diminish under the influence of a variety of diseases As judged by experiments with radioactive iodine, it appears that iodides (but not thyroxin-iodine) tend to accumulate in the pituitary following their introduction into the body. Yet the iodine affinity of the hypophysis is far below that of the thyroid

The *bromine* content of fresh pituitary tissue varies between 0 4 to 0.8 mg % and — contrary to earlier reports in the literature — it is not significantly higher than in other tissues

The *zinc* content of human pituitary tissue is claimed to be very high (112 mg./100 gm. of dry weight), but this requires confirmation.

Among other inorganic constituents, *calcium, phosphate, sulphur, manganese, iron and even traces of arsenic* have been demonstrated in pituitary tissue, their concentration here is approximately the same as in most other tissues

The WATER content of the pituitary varies between 74-80% in the various species. It is claimed that the posterior-lobe contains slightly more water than the anterior-hypophysis.

The ASCORBIC ACID content of cattle anterior-lobe (1.95 mg./gm. of fresh tissue) is significantly higher than in the posterior-lobe (0.46 mg./gm.). It is noteworthy that the hypophysis (like the adrenal cortex) is one of the organs containing the highest concentration of ascorbic acid; it loses this substance under the influence of a variety of non-specific damaging agents

CHOLINE, ACETYLCHOLINE AND HISTAMINE have also been demonstrated in pituitary tissue, because of certain similarities in the pharmacologic actions of these compounds and those of posterior-lobe hormones, earlier investigators believed that the former are largely responsible for the biologic actions of posterior-lobe preparations This has been disproven, but the biologic significance of these compounds in the pituitary is not yet known.

Among other compounds, whose presence has been demonstrated in the hypophysis are · GLUTATHIONE, a variety of VITAMINS, ENZYMES, and CAROTENE It is interesting that the posterior-lobe, which is comparatively rich in lipids, also contains more lipase than the anterior-hypophysis

CLASSIFICATION AND CHEMISTRY OF THE HYPOPHYSEAL HORMONES

Classification of the Anterior-Lobe Hormones. — The anterior-pituitary produces a large number of hormones,

(4) THE ANTILUTEOGENIC ACTION. After hypophysectomy, the involution of corpora lutea is slow, especially in certain animal species (e.g., rat). It can be accelerated, however, by impure anterior-pituitary extracts Hence, it has been postulated that the latter contain a hypothetic "antiluteogenic hormone" which accelerates the regression of corpora lutea. It has since been demonstrated, however, that both purified FSH and LH preparations have a similar effect, especially if administered by the intraperitoneal route.

(5) THE THYMOTROPHIC ACTION Gonadotrophins and ACTH cause thymus involution because they liberate steroids (from the gonads and adrenal cortex respectively) which possess antithymic effects. Certain crude anterior-lobe extracts, however, tend to increase the size of the thymus. This led to the belief that a special "thymotrophic hormone" may be secreted by the anterior-lobe. The thymotrophic effect has now been duplicated with the pure somatotrophin preparations and it is doubtful whether it should be ascribed to a special hormone. It is known, furthermore, that short-term treatment with very high doses of desoxycorticosterone acetate causes thymus involution while prolonged administration of the same compound in small doses actually increases thymic weight. This may be due to the resulting compensatory atrophy of the adrenal cortex and the consequent reduction in the elaboration of the more potent anti-thymic cortical hormones. Some such mechanism may well be responsible for the thymotrophic effect of anterior-pituitary extracts, hence the existence of the special thymotrophic hormone" remains to be demonstrated.

(6) THE RENOTROPHIC ACTION. Certain impure anterior-pituitary extracts enlarge the kidney disproportionately, that is to say, more markedly than could be expected on the basis of their somatotrophin content. Although the existence of a special renotrophic hormone has never been postulated, this possibility suggests itself, especially since pure somatotrophin causes no disproportionate renal growth. It must be kept in mind, however, that the most active renotrophic anterior-pituitary preparations also exert definite hepatotrophic and other splanchnotrophic actions, so that the effect is not entirely specific. In thyroidectomized animals, all these actions are greatly diminished, but not abolished. This proves that they are not merely due to the thyrotrophic-hormone content of the extracts and the resulting increased thyroid-hormone secretion. Gonadectomy and adrenalectomy likewise fail to prevent the kidney-stimulating effect of anterior-lobe extracts, hence, this action cannot be ascribed to renotrophic, gonadal or adrenal hormones (e.g., testoids). Further work with purified anterior-pituitary hormones will be necessary to establish whether the renotrophic, hepatotrophic and other splanchnotrophic actions of impure extracts are due to special splanchnotrophic hormones or to combinations of several of the already authenticated anterior-lobe principles (e g., a combined effect of somatotrophic plus thyrotrophic homones).

(7) THE NEPHROSCLEROTIC ACTION. Certain impure anterior-pituitary extracts cause nephrosclerosis and hypertension The renal lesions so produced are strikingly similar to those elicited by overdosage with desoxycorticosterone acetate, except that they are complicated by the simultaneous production of the renotrophic effect, presumably due to the impurity of the anterior-pituitary preparations employed. The existence of a special nephrosclerotic pituitary-hormone has never been postulated The bulk of evidence suggests that anterior-pituitary extracts cause nephrosclerosis through the intermediary of the adrenal, by virtue of their corticotrophic-hormone content. The possibility must also be considered that several anterior-pituitary hormones may cooperate in the production of nephro-

tion of the adrenal cortex, both in intact and in hypophysectomized animals. It tends to deplete the cortex of its lipid and ascorbic acid content. It has no effect upon the adrenal medulla. Only anterior-lobe tissue contains significant amounts of this principle. (See p. 212.)

(5) THYROTROPHIC HORMONE (TTH). *Synonyms*: thyrotrophin, thyreotrophic hormone. This hormone has not been isolated. Its most characteristic action is to stimulate the growth and thyroid hormone secretion of the thyroid gland, in intact and hypophysectomized animals. Significant amounts of it occur only in anterior-lobe tissue.

(6) SOMATOTROPHIC HORMONE (STH). *Synonyms*: somatotrophin, growth hormone. This principle has been crystallized. Its chief characteristic is to stimulate somatic growth in general, both in intact and in hypophysectomized animals. As long as the epiphyseal junction cartilages are still open, it causes the skeleton to grow both in length and in thickness; it also promotes the development of soft tissues. After ossification is completed, it can no longer stimulate growth in length, but retains its other effects. It does not cause selective growth of any one organ This principle occurs in significant amounts only in anterior-lobe tissue.

A number of actions of impure anterior-hypophyseal extracts have not been proven to be caused by special hormones. — Some of these have been, or still are, alleged to be produced by principles distinct from the above-mentioned six authenticated anterior-lobe hormones, for others, no such definite claim has been made. We shall enumerate the most important actions of this type, in order to avoid possible confusion arising from unjustified claims in the earlier literature; the list will also call attention to the potential existence of additional anterior-lobe hormones

(1) THE OVULATION-INDUCING ACTION. — FSH causes maturation of the follicles, while LH transforms them into corpora lutea. Under ordinary conditions of experimentation, this results in the formation of atretic corpora lutea, with enclosed ova, due to lack of ovulation. Certain gonadotrophic preparations, however, elicit ovulation and this led to the belief that they contain a special "ovulation-inducing hormone." It is now almost generally agreed, however, that under optimal experimental conditions, LH itself can produce ovulation following pretreatment with FSH, in several animal species. Other species (e.g., man) are singularly refractory to this effect, but they also fail to respond to impure extracts, allegedly containing the "ovulation-inducing hormone" Hence, it is unnecessary to postulate the existence of a special principle to explain this action

(2) THE SYNERGISTIC ACTION. It has been claimed that, in females, the gonadotrophic effect of LH preparations can be greatly augmented by certain anterior-lobe extracts, which do not contain demonstrable amounts of gonadotrophins. This was attributed to a hypothetic "synergist" or "augmenting factor," presumed to be a hormone It is now agreed, however, that this synergistic effect was due to sub-threshold amounts of FSH in the anterior-pituitary preparations used.

(3) THE ANTAGONISTIC ACTION Certain anterior-pituitary extracts, when given intraperitoneally, antagonize the gonadotrophic action of simultaneously, subcutaneously administered gonadotrophic extracts. This effect has been attributed to the presence, in the anterior-lobe extracts, of an "antagonist" or "atresin"; a hormone which causes follicular atresia and inhibits the action of gonadotrophins. It has since been demonstrated, however, that even purified FSH or LH preparations, when given by the intraperitoneal route, antagonize the trophic effect of subcutaneously administered gonadotrophic extracts. Hence, it is no longer necessary to invoke the existence of this principle

(4) THE ANTILUTEOGENIC ACTION. After hypophysectomy, the involution of corpora lutea is slow, especially in certain animal species (e.g., rat). It can be accelerated, however, by impure anterior-pituitary extracts. Hence, it has been postulated that the latter contain a hypothetic "antiluteogenic hormone" which accelerates the regression of corpora lutea. It has since been demonstrated, however, that both purified FSH and LH preparations have a similar effect, especially if administered by the intraperitoneal route.

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sclerosis, especially because previous thyroidectomy diminishes, while thyroid hormone treatment augments the nephrosclerotic action of the impure anterior-lobe extracts. Even other metabolic hormones of the anterior-lobe may be involved in this effect, particularly since it has been established that high-sodium, high-protein diets augment, while acidifying salts and *certain sugars antagonize the nephrosclerotic properties of the anterior-pituitary extracts.*

(8) THE GLUCO-CORTICOTROPHIC, MINERALO-CORTICOTROPHIC, LIPOCORTICOTROPHIC AND TESTO-CORTICOTROPHIC ACTIONS. It is known that the adrenal cortex produces gluco-corticoids (e.g., corticosterone), mineralo-corticoids (e.g., the "sodium factor," which resembles desoxycorticosterone in its actions), testoids (e.g., dehydro-iso-androsterone, adrenosterone) and perhaps *even fat deposition-stimulating lipo*-corticoids. Clinical experience indicates that all these hormones are not necessarily produced in set proportions, but that under varying conditions, one or the other type may predominate It is known, furthermore, that testoids can *cause selective atrophy of the reticularis* (the testoid-producing zone) in females, while experiments on male castrates revealed that stimulation of the adrenal cortex, by folliculoids or alarming stimuli, causes a pronounced increase in the production of life-maintaining corticoids, without the slightest increase in endogenous testoid production. *Since the function of the adrenal* cortex is under the influence of the anterior-pituitary, it is tempting to assume that the latter can produce various corticotrophins, which selectively stimulate one or the other function of the adrenal cortex. It must be admitted, however, that the adrenocorticotrophic hormone (ACTH) *now available*, exhibits all the characteristics of a pure protein and the existence of different types of corticotrophins *has not been* proven It is possible that the same pituitary trophic principle exerts different actions, depending upon the simultaneous *presence of other hormones* (e.g., steroids). Further experimentation with pure preparations will be necessary to elucidate this point, but it is well to keep in mind the possibility of several corticotrophins and the certainty of several corticotrophic effects.

(9) THE ADRENOMEDULLOTROPHIC ACTION. *It has been claimed that certain anterior-pituitary extracts selectively stimulate the growth and hormone production of the adrenal medulla. These claims have not been substantiated.*

(10) THE PARATHYROTROPHIC ACTION. Following the administration of impure anterior-pituitary extracts, the parathyroids tend to enlarge in certain animal species. This effect is very inconstant, and contrary to earlier claims, hypophysectomy causes no significant atrophy of the parathyroids *Although* some investigators postulated the existence of a special "parathyrotrophic hormone," this is hardly justified on the basis of available evidence. The enlargement of the parathyroids, occasionally noticed following anterior-pituitary extract treatment, *could* well be secondary to the metabolic changes induced by these preparations It is known that renal lesions, rachitogenic diets and bone destruction due to a variety of other causes, produce secondary parathyroid enlargement, not unlike that caused by "parathyrotrophic" anterior-pituitary extracts

(11) THE MAMMOGENIC ACTION Impure anterior-pituitary extracts stimulate the growth of the mammary glands This effect is distinctly different from that of the luteotrophic (or "mammotrophic") hormone, which merely causes secretion, but not development of the breast. Since folliculoid, testoid and luteoid steroids cause marked breast growth only in the presence of the pituitary, it is tempting to assume that the *anterior-lobe produces a special mammogenic* principle, whose elaboration

would be increased by the above-mentioned steroids. *It must be kept in mind*, however, that certain steroids can slightly stimulate breast growth, even in the absence of the anterior-lobe; hence, the *mammogenic effect* may merely be due to a potentiation of the mammogenic action of steroids, by a pituitary principle. None of the pure anterior-lobe hormones have been shown to possess such a mammogenic effect, but the existence of a special, "mammogenic hormone" has not been proven.

(12) THE GLYCOTROPIC OR ANTI-INSULIN ACTION. Impure anterior-pituitary extracts induce an insensitivity to the action of insulin, both in intact and in hypophysectomized animals. This effect is not seen after adrenalectomy, and similar actions can be elicited by ACTH and gluco-corticoids; hence it is highly probable that the anti-insulin effect of anterior-lobe extracts is mediated by the gluco-corticoids, which increase the glycogen stores in the liver and thus provide more sugar to antagonize insulin-hypoglycemia

(13) THE GLYCOSTATIC ACTION Under certain conditions, anterior-pituitary extracts restore the ability of fasting hypophysectomized animals to preserve their glycogen stores. Since muscle glycogen can thus be maintained even following adrenalectomy, the effect is not mediated by the gluco-corticotrophic principle It has been ascribed to a special "glycostatic factor," as this effect is not associated with any of the authenticated anterior-lobe compounds. However, corticoids greatly potentiate this action and it is not impossible that the effect is due to one of the known anterior-lobe hormones or to synergistic combinations of these.

(14) THE PANCREATOTROPHIC ACTION. It has been found that repeated treatment with impure anterior-pituitary extracts can cause an increase in the size, number and insulin content of the Langerhans islets in the rat. It has therefore been assumed that the anterior-pituitary produces a trophic substance, which augments the morphologic development and insulin production of the islet tissue. It is noteworthy, however, that hypophysectomy does not cause any significant involution of the Langerhans islets. The possibility must be kept in mind that the stimulation of the islets may merely be a secondary, compensatory reaction, such as is noted for instance on high carbohydrate diets or following partial ablation of the pancreas. Further work will be necessary to establish whether there is a special pancreatotrophic hormone or whether the pancreatotrophic effect merely represents a compensatory reaction to the metabolic derangements caused by anterior-pituitary-hormone overdosage.

(15) THE DIABETOGENIC ACTION. Sometimes following prolonged treatment with impure anterior-pituitary extracts, a state of permanent diabetes develops in experimental animals (e.g., dog). The Langerhans islets are at first stimulated (pancreatotrophic effect?), but later destroyed, by repeated injections of the active material. Simultaneously, the insulin content of the pancreas gradually diminishes to a negligible quantity. The diabetic state so produced is not intensified by complete pancreatectomy. Unlike the depancreatized dogs, those in which the diabetes is produced by diabetogenic, hypophyseal extracts can survive for long periods without insulin treatment.

The diabetogenic activity of anterior-lobe extracts is associated with the globulin and pseudoglobulin fractions, but isolation of the active material has not yet been accomplished. It appears that the effect depends upon an "exhaustion" of the islet tissue, since the destruction of the pancreatic islets is preceded by a period of hyperplasia and hypertrophy; insulin counteracts this, while over-feeding (especially with carbohydrate diets) and partial pancreatectomy sensitize to the diabetogenic effect. Further experiments will have to show whether this action is merely a result of metabolic derangements

sclerosis, especially because previous *thyroidectomy* diminishes, while thyroid hormone treatment augments the nephrosclerotic action of the impure anterior-lobe extracts. Even other metabolic hormones of the anterior-lobe may be involved in this effect, particularly since it has been established that high-sodium, high-protein diets augment, while acidifying salts and certain sugars antagonize the nephrosclerotic properties of the anterior-pituitary extracts.

(8) THE GLUCO-CORTICOTROPHIC, MINERALO-CORTICOTROPHIC, LIPOCORTICOTROPHIC AND TESTO-CORTICOTROPHIC ACTIONS. It is known that the adrenal cortex produces gluco-corticoids (e.g., *corticosterone*), *mineralo-corticoids* (e.g., the "sodium factor," which resembles desoxycorticosterone in its *actions*), *testoids* (*e g., dehydro-iso-androsterone*, adrenosterone) and perhaps even fat deposition-stimulating lipo-corticoids. Clinical experience indicates that all these hormones are not necessarily produced in set proportions, but that under varying conditions, one or the other type may predominate. It is known, furthermore, that testoids can cause selective atrophy of the reticularis (the testoid-producing zone) in females, while experiments on male castrates revealed that stimulation of the adrenal cortex, by folliculoids or alarming stimuli, causes a pronounced increase in the production of life-maintaining corticoids, without the slightest increase in endogenous testoid production. Since the function of the adrenal cortex is under the influence of the anterior-pituitary, it is tempting to assume that the latter can produce various corticotrophins, which selectively stimulate one or the other function of the adrenal cortex. It must be admitted, however, that the adrenocorticotrophic hormone (ACTH) now available, exhibits all the characteristics of a pure protein and the existence of different types of corticotrophins has not been proven. It is possible that *the same* pituitary trophic principle exerts different actions, depending upon the simultaneous presence of other hormones (e.g., steroids). Further experimentation with pure preparations will be necessary to elucidate this point, but it is well to keep in mind the possibility of several corticotrophins and the certainty of several corticotrophic effects

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fall into two groups : the glycoproteins (thyrotrophin, FSH and LH) and the simple proteins or polypeptides (somatotrophin, corticotrophin and luteotrophin). Generally speaking, somatotrophin and luteotrophin are water-insoluble proteins, while FSH, LH and thyrotrophin are highly soluble in water; ACTH is intermediate.

The most outstanding physico-chemical and analytic data of pure preparations of LH, corticotrophin, luteotrophin and somatotrophin are summarized in the two tables below :

Physico-chemical properties of LH (ICSH), corticotrophin (ACTH), luteotrophin (lactogenic hormone) and somatotrophin (growth hormone)

(after C.-H. Li, Ann. Rev. Biochem. 1947)

Determination	ICSH		ACTH		Lactogenic Hormone		Growth Hormone (Ox)
	Sheep	Swine	Sheep	Swine	Sheep	Ox	
N, %	14 2	14 93	15 65	15 47	15 86	16 50	15 65
S %			2.3	2 33	1 79	2 0	1 3
Cystine, %			7 19		3 11	3 4	2.25
Methionine, %			1 93		4 31		3 06
Tryptophane, %	1 0	3 8			1.25	1.3	0 84
Tyrosine, %	4 5				4 53	5 7	4.3
Molecular Weight M							
Osmotic Pressure	40 000				26 500	26,500	44,250
Sedimentation		100 000	20 000	20,000		32 000	
Diffusion constant, $D_{20} \times 10^7$			10 4		9 0	7.5	7 15
Sedimentation constant as Svedberg units, S	3 6	5 4	2 08	2 04-2 11		2 65	
Isoelectric Point, pH	4 6	7 45	4 65-4 70	4 70-4 80	5 73	5 73	6 85
Partial specific volume, V_1					0 721		0 760
Relative viscosity					6 65		7.64
Dissymmetry constant, f/f_0			1 1		1 29		1 31

The amino-acid composition of the various anterior-lobe hormones appears to be essentially similar to that of other tissue proteins. As far as we know, these hormones are not characterized by the presence of any amino-acid which would not occur in other tissues in approximately similar quantities. As an example we cite the composition of somatotrophin in the table below.

Composition of Somatotrophin

(after C.-H. Li, Ann. Rev. Biochem. 1947)

Constituent	N as % Protein N	Amount per 100 gm protein	Minimal Mol Wt	Assumed number of residues	Calculated Mol Wt.
Amide-N (Ammonia)	6 3	1 2	1420	30	(42 600)*
Arginine	18 8	9 1	1910	25	47,700
Aspartic-Acid	6 1	9 0	1480	32	47,300
Cystine	1 7	2 25	10700	4	(42,808)*
Glutamic Acid	7 9	13 0	1130	42	47,400
Glycine	4 5	3 8	1980	24	47 400
Histidine	4 6	2 65	5850	8	46 800
Isoleucine	2 7	4 0	3780	14	46,000
Leucine	8 3	12 1	1080	44	47,700
Lysine	8 7	7 1	2060	23	47,400
Methionine	1 7	2 9	5140	9	46 200
Phenylalanine	4.3	7 9	2090	23	48 000
Threonine	6 8	9 0	1320	36	47,600
Tryptophane	0 7	0 84	24500	2	48 700
Tyrosine	2 1	4 3	4220	11	46,400
Valine	3 0	3 9	3000	16	48 000
Total found	88 2	93 04		343	
Mean ± Standard deviation					47,300 ± 600

* Values in bracket are omitted from the mean

(which cause a secondary breakdown of the Langerhans islets due to their inability to compensate indefinitely), or whether we are dealing with a direct hormone action upon the islet tissue. It is also questionable whether the diabetogenic action is caused by a single hormone or by combinations of several known metabolic principles.

(16) THE ANTI-DIABETIC EFFECT OF ORALLY ADMINISTERED ANTERIOR-LOBE PREPARATIONS. Earlier claims that certain pituitary extracts elicit an anti-diabetogenic effect in pancreatectomized animals and in diabetic patients when given by mouth, have not been substantiated.

(17) THE CONTRA-INSULAR ACTION. Impure anterior-pituitary extracts cause hyperglycemia in the dog, especially when injected directly into the cerebrospinal fluid. From this it was concluded that a special "Kontrainsulares Hormon" is elaborated by the anterior-lobe and acts directly upon the "carbohydrate-metabolism centers" of the brain. The evidence supporting this concept is unconvincing and it appears very probable that the effect is due to direct nervous irritation by toxic substances in the extract with a consequent discharge of adrenaline.

(18) THE KETOGENIC ACTION. Impure anterior-pituitary extracts increase ketonemia in experimental animals It is highly doubtful whether this is due to a special "ketogenic" or "fat-metabolism hormone" ("Fettstoffwechsel Hormon"), rather than to the diabetogenic effect, perhaps in conjunction with other metabolic hormones. The dependence of the ketonemia upon the adrenal cortex suggests the possibility that ACTH may also be involved.

(19) THE FATTY-LIVER-PRODUCING ACTION. Hypophysectomy prevents fat deposition in the liver, under various experimental conditions (e.g., partial hepatectomy and fasting, certain diets) which normally cause fat migration from the tissues into the hepatic cells Treatment of hypophysectomized animals with impure anterior-lobe extracts restores their ability to form fatty livers, and overdosage with such pituitary preparations may, in itself, suffice to cause fat infiltration in the liver. The available evidence does not suffice to postulate the existence of a special, fatty-liver-producing pituitary principle. It is especially noteworthy that adrenalectomy also prevents the production of fatty livers under similar conditions, hence the ACTH probably plays an important part in conditioning this action of anterior-lobe preparations.

(20) THE PREPUTIAL GLAND-STIMULATING ACTION. Impure anterior-pituitary extracts stimulate the growth of the preputial glands, especially in rodents. This effect is not mediated by the gonads, as it can be produced in castrates, yet certain steroids, not necessarily testoids (e.g., pregnenolone), potentiate the preputial gland-stimulating action of the anterior-lobe preparations Since the preputial gland is merely a modified (and readily measurable) sebaceous gland, the effect may be related to the sebaceous gland-stimulation and acne of hyperpituitarism We do not know which hormone(s) is responsible for this effect.

(21) OTHER ACTIONS ALLEGEDLY DUE TO SPECIAL HORMONES A number of other actions have been ascribed to special anterior-lobe hormones, on the basis of very insufficient evidence Among these are the *restropic* (reticulo-endothelial-system stimulating), the *hemopoiesis-stimulating action*, the *ketonemia-decreasing*, the *blood-pressure-depressing* the *protein-metabolism-stimulating*, the *deaminizing* and the *thyroid-depressing* hormones The latter action is allegedly elicited only by the pituitaries of rats fed with thyroid hormone

Chemistry of Anterior-Lobe Hormones. — A detailed discussion of the extremely complex chemistry of the anterior-lobe hormones would be far beyond the scope of this textbook. Suffice it to say, that chemically, the six authenticated anterior-lobe principles

Among the ENZYMES, crystalline pure trypsin destroys the activity of LH more readily than that of FSH, while pepsin tends to destroy FSH more readily than LH, but only upon prolonged reaction. Ptyalin selectively abolishes FSH activity, LH being much more resistant.

(2) LUTEOTROPHIN. UREA greatly increases the viscosity of luteotrophin without permanently inactivating it, since, if the urea is removed by dialysis, the original viscosity and activity return to normal DETERGENTS of the sodium alkylarylsulfonate-type (Nacconol) likewise reversibly increase the relative viscosity and diminish the activity of the hormone.

Luteotrophin is destroyed by certain ENZYMES (pepsin and trypsin). In the absence of salt, at pH 8.0 luteotrophin shows little loss in potency after boiling for one hour; it is more resistant to heat in acid than in alkaline solution.

(3) CORTICOTROPHIN. KETENE acetylates both the phenolic and the amino-groups of corticotrophin; this diminishes its hormonal activity. Here again, it is assumed that the biologic action is, at least partly, dependent upon the free amino-groups. That free amino-groups are essential for the activity of corticotrophin is also shown by other observations Thus, compounds which attack these groups (e g., NITROUS ACID and FORMALDEHYDE) readily destroy the potency of corticotrophin

The IODINE uptake of the hormone corresponds roughly to its tyrosine content; since during iodinization, the biologic potency is diminished, tyrosine groups appear to be essential for the corticotrophin action.

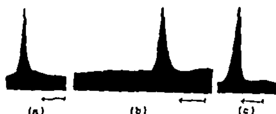
Partial digestion of corticotrophin with ENZYMES yielded most interesting results. With trypsin, no significant diminution in corticotrophin activity is observed until about 18% and with pepsin until about 50% of the hormone is hydrolyzed. This indicates that the products of hydrolysis whose molecular weight is lower than that of the hormone (presumably polypeptides), still possess corticotrophic activity.

(4) SOMATOTROPHIN. Denaturation of somatotrophin by treatment with UREA does not influence its growth-promoting potency. From the loss of activity following treatment with NITROUS ACID and KETENE, it was concluded that here again free, primary amino-groups are essential for the hormonal potency. Proteolytic ENZYMES, such as trypsin or pepsin, greatly diminish the potency of somatotrophin upon incubation at 37° C. Somatotrophin is rather heat-sensitive. Activity is completely lost at pH 4 0-8.9 following boiling for 10 minutes. It is somewhat more stable in alkaline than in acid solutions

Chemistry and Biologic Characteristics of Intermedin. — INTERMEDIN (*Synonyms* · middle-lobe hormone, chromatophorotrophic hormone, melanophore-expanding principle, B-hormone), is a protein-like substance found in the middle or intermediate-lobe of the pituitary, in animals in which there is an anatomically distinct structure of this type. Similarly, tissue cultures of intermediate-lobe cells are rich in this substance, while those of the anterior or posterior-pituitary are free of it, or contain only traces which may have entered it by diffusion from the intermediate-lobe. Such secondary diffusion is probably also responsible for the presence of intermedin in the simple posterior-lobe extracts (e.g., "pituitrin") commonly in clinical use. In those species which possess no distinct pars intermedia (e.g., porpoise, whale, fowl), intermedin is found only in extracts of the anterior-lobe, not in those of the posterior-pituitary. On the basis of all these observations, it has been assumed that intermedin is a distinct hormone, elaborated by the intermediate-lobe cells or, in species in which there is no middle-lobe, by the anterior-lobe cells

In poikilothermic animals (e g., toad, frog), whose skin contains contractile

Since electrophoresis is frequently used as a method for the determination of homogeneity in protein hormone preparations (see: General Endocrinology, p. 27) we show the electrophoresis patterns of pure somatotrophin as an example:



Electrophoresis patterns of the ascending boundary of somatotrophin preparations
(Courtesy of Dr C H Li)

(a) acetate buffer of pH 4 0, 120 minutes electrolysis.
(b) acetate buffer of pH 4 95, 540 minutes electrophoresis.
(c) barbiturate buffer of pH 9 60 All buffers of 0 10 ionic strength, 1 5°C



Somatotrophin (the growth hormone) as it appears at a magnification of 150.
(Courtesy of Dr C H Li)

It will be noted that the hormone migrates as a single component in all three buffer solutions. If the protein in the three sections of the electrophoresis cell is separately recovered, no difference in growth potency of the three fractions is noted. The homogeneity of the preparation with regard to its electro-chemical properties is thus demonstrated by the impossibility to achieve separation by electrophoresis.

Somatotrophin has recently been crystallized from a dilute solution of 15% ethanol at 2°C. The crystals appeared as thin plates and were highly soluble at room temperature. They are shown on this page.

As regards the RESISTANCE OF HYPOPHYSEAL HORMONES TO VARIOUS AGENTS, the following facts are noteworthy:

(1) FSH and LH. — PROTEIN PRECIPITANTS (picric acid, picrolonic acid, flavianic acid) are claimed to inactivate FSH, in concentrations which do not affect LH. Allegedly 2 5% trichloracetic acid completely precipitates LH, but not FSH. Further work with pure hormone preparations will be necessary, however, since these claims have not been uniformly confirmed.

CYSTEINE, which reduces -S-S- linkages in proteins, does not readily inactivate FSH and LH preparations since the disulphide-bonds of these protein-hormones are less reactive in this respect than those of many other proteins. However, upon long continued reaction with cysteine, this type of inactivation does occur.

KETENE is a mild acetylating agent, which attacks the amino, phenolic hydroxyl and sulfhydryl group in aqueous protein solutions FSH is comparatively resistant, while LH is rapidly inactivated during the process of ketene acetylation It is assumed that this inactivation is due to the acetylation of the free amino-groups, and that the amino-groups are essential for activity, but this has not yet been definitely proven

companies. Consequently, a clear-cut distinction between trade names and scientific names is somewhat difficult.

(1) VASOPRESSIN. *Synonyms* : vasopressor principle, postlobin-V, pitressin, vasopressor-anti-diuretic principle. The hormone has not been isolated, but some preparations contain as much as 200 pressor units (and only 10 oxytocic units) per mg. Such highly purified pressor preparations have been proven to contain arginine, proline, isoleucine, cysteine and tyrosine. Histidine, hydroxyproline and glycine were shown to be absent, while tryptophane is present only in traces, if at all. The activity is readily destroyed by hydrolysis with dilute acid or alkali, active reducing agents and the enzymes of the gastrointestinal tract.

The "*anti-diuretic hormone*" of the posterior-pituitary is probably identical with vasopressin, since claims concerning the separation of these two activities have not been confirmed

(2) OXYTOCIN. *Synonyms* oxytocic hormone, oxytocic posterior-lobe principle, postlobin-O, pitocin. The chemical and physical properties of oxytocin are very similar to those of vasopressin. Hence the separation of the two hormones is difficult. Oxytocin has not yet been isolated, but highly purified preparations contain as much as 250 oxytocic units (and only 5 pressor units) per mg. The amino-acid composition of these highly purified preparations is almost the same as that of vasopressin, except that they appear to contain leucine instead of isoleucine. Oxytocin is readily destroyed by an enzyme ("pitocinase") contained in human blood Since the blood-concentration of this enzyme rises rapidly during the first weeks of gestation, it may even act as an indicator in the diagnosis of pregnancy.

It is noteworthy that simple posterior-pituitary extracts inhibit diuresis only when the osmotic pressure of the urine is low. The same preparations exert a *diuretic action*, at times when urine with a high osmotic pressure is excreted. Both diuretic and anti-diuretic actions are accompanied by increased urinary elimination of certain salts. This led to the assumption that the diuretic action is dependent upon the salt output. If posterior-lobe extract is given when the salt concentration in the urine is already high, the increase in salt excretion necessitates a further rise in water output. If rats are given much water by stomach tube, 0 0001 oxytocic units per 100 gm. of body weight of a highly purified oxytocin preparation, have a definite diuretic action. This quantity of the substance weighs only 0 0000004 mg It seems very improbable that the diuretic action is due to a contamination in this quantity of material. Probably it is oxytocin which causes diuresis in hydrated animals, while vasopressin elicits merely "salt-diuresis" after dehydration, and only at low dose levels.

GENERAL PHARMACOLOGY OF THE HYPOPHYSEAL HORMONES

STANDARDIZATION

Analytic Methods for the Detection of Hypophyseal Hormones. — There are no satisfactory analytic methods for the determination of any of the anterior, middle or posterior-lobe hormones. All these principles are estimated by bioassay.

Bioassay of the Follicle-Stimulating Hormone. — The INTERNATIONAL UNIT (I.U.) of FSH is defined as the specific gonadotrophic activity of 250γ of a standard pregnant-mare-serum preparation kept at the Department of Biological Standards, National Institute for Medical Research, London, England. It is recommended only for the assay of gonadotrophic preparations of the serum of pregnant mares Recent progress in the purification of FSH will necessitate

pigment cells (chromophores or chromatophores), the function of this hormone appears to be clearly established. Injection of intermedin causes the pigment granules in the melanophores to become dispersed throughout the bodies and branches of these cells, thus causing a darkening of the skin. For instance, in the frog, whose chromatophores ("melanophores") contain black granules of melanin, intermedin causes the skin to become coal black. In other species, in which the chromatophores contain red ("erythrophores") or yellow ("xanthophores") pigment granules, the hormone produces a red or yellow coloration respectively. Since in these same species, hypophysectomy causes blanching of the skin, while intermedin restores its color to normal, the substance appears to represent a physiologic hormonal principle regulating skin coloration. Not only the distribution, but even the production of melanin in the skin of the frog is allegedly stimulated by intermedin. It has also been claimed to accelerate the oxidation of the pigment producing tyrosine-tyrosinase system in vitro.

The rôle of intermedin in mammals, especially its influence upon cutaneous pigmentation in man, is still a debated problem.

Treatment with alkali greatly increases the potency of intermedin. The most purified preparations cause definite darkening of the frog's skin at a dose level of 0.005γ and are 73 times as active as the standard posterior-pituitary powder. They are practically free of oxytocin and vasopressin. They contain tyrosine, arginine and cysteine.

Chemistry and Biologic Characteristics of the Posterior-Lobe Hormones. — Posterior-lobe extracts exert three chief activities: they raise the blood pressure (due to their vasoconstrictor effect), they cause uterine contractions and they diminish diuresis. Separation of the oxytocic and vasopressor actions by chemical means is possible, but whether the anti-diuretic activity can be separated from vasopressor extracts is very doubtful. It is generally agreed therefore that there are at least two distinct posterior-lobe principles, the oxytocic and the vasopressor hormones respectively; the latter probably being responsible for the antidiuretic action. Some investigators believe that these two fractions are artefacts and due to the breakdown in the course of the extraction procedure of an originally single principle, but this view has not been proven. The compounds appear to be polypeptides, with a comparatively small molecular weight of about 2,000. The usual commercially available "posterior-pituitary injection" or "pituitrin" preparations are simple extracts containing all three activities.

It is also debatable whether the posterior-lobe principles are true hormones, in the sense of the definition given under "General Endocrinology" (p. 11). Some investigators regard them as pharmacologically active tissue extracts, which do not perform any physiologic, hormonal functions. This view is mainly based upon the comparatively vague deficiency syndrome, following extirpation of the posterior-lobe and the apparently non-glandular nature of the neuro-hypophysis. Yet, the pituicytes may well be the producers of true hormones and the absence of pronounced posterior-lobe-deficiency symptoms following complete hypophysectomy is probably due to the simultaneous ablation of the anterior-lobe, whose presence appears to aggravate posterior-lobe deficiency. Furthermore, cells of the tuber cinereum and of the adjacent hypothalamic region can perhaps partly compensate for the lack of the pars neuralis.

It is regrettable that many of the scientific terms used for the designation of crude pituitary extracts or purified posterior-lobe fractions, have frequently been employed to designate specific products sold by various pharmaceutic

mentioned action of LH and hence, contamination with FSH does not interfere with the results.

Another bioassay technic is based upon the morphologically detectable *stimulation of the Leydig cells* by LH in hypophysectomized male rats.

The increase in the OVARIAN WEIGHT, LEYDIG-CELL DEVELOPMENT OF SEMINAL VESICLE WEIGHT IN INTACT IMMATURE RATS, the MELANIN DEPOSITION IN THE BREAST FEATHERS of the African weaver finch, etc, have also been recommended as indicators; however, these technics are less specific than the assay on hypophysectomized animals, mainly because the endogenous production of gonadotrophins by the pituitary can obscure the results.

Bioassay of Comparatively Impure Gonadotrophin Preparations. — Most of the above-mentioned technics are too complicated or time-taking for clinical purposes; hence, several simpler bioassay methods have been developed for the routine estimation of gonadotrophins in blood and urine. Although these are not sufficiently specific or sensitive for the assay of purified FSH or LH, they are useful in the study of clinical problems. The following are of special value

(1) THE ASCHHEIM-ZONDEK TEST (1929), as originally described, is performed on a group of five, 3 to 4-week-old female, white mice, each weighing 6-8 gm. To 25-30 cc. of a morning sample of urine, one drop of tricresol is added as a preservative, and then it is slightly acidified with a few drops of 10% acetic acid. The urine thus prepared is injected subcutaneously twice daily on three consecutive days, each mouse receiving a total of 6 injections. The individual doses, each given 6 times to one of the 5 animals, are : 0 2, 0 25, 0.3, 0 35 and 0 4 cc Autopsy is performed 96 hours after the first injection If time permits, the ovaries are examined histologically, but usually, examination with a magnifying lens suffices. The test is considered positive if there is a single hemorrhagic follicle, the so-called "Blutpunkt" (anterior-pituitary reaction or "APR" II) or corpus luteum (APR III) in any of the test animals. The finding of mature, but unruptured and not luteinized follicles (APR I), indicates the presence of FSH. The test is especially useful in the early diagnosis of pregnancy, chorionepitheliomas and hydatidiform moles, all of which cause a positive LH reaction (APR II or III), while the urine of castrates tends to elicit only follicle maturation (APR I) due to its high FSH content. (See also pp. 377, 378.)

The major objections to this test, as originally devised, are that it is rather time-taking and that the urine is sometimes so toxic that it kills the experimental mice. Hence, many modifications have been developed (see below) in an effort to partially purify the gonadotrophic preparations used for assay and to improve experimental conditions, in order to obtain more rapid results.

(2) The OVARIAN HYPEREMIA TEST is based upon the fact that LH causes marked hyperemia of the ovary, as early as 2-6 hours after injection. This reaches a maximum after 24 hours and disappears in 48 hours. Since this hyperemia precedes the formation of follicles or corpora lutea it can act as an early indicator of LH activity. The hyperemia is apparently due to LH, although FSH seems to act as an augmenting factor. The test is particularly useful in the rapid, early detection of pregnancy (e.g., in cases suspected of ectopic gestation, where an immediate decision must be made about the necessity of a surgical intervention). Several technics are in use. *Zondek et al.* (1945) designated as "one hyperemia unit that amount of gonadotrophic hormone which induces hyperemia of the whole ovary in an infantile female rat within 24 hours."

For this modification, the infantile rat proved preferable to the mouse. A

the establishment of a revised and more generally applicable I.U

The most satisfactory test-object for the bioassay of FSH is the HYPOPHYSECTOMIZED RAT. In *females* deprived of their pituitaries, pure FSH preparations cause only follicle maturation without luteinization or stimulation of the degenerated theca cells ("wheel cells"). One rat unit is defined as the minimal total amount which, given in three, daily, subcutaneous injections to hypophysectomized rats (26-28-day-old at operation and 6-8 days postoperative when injections are commenced), causes appearance of normal, non-atretic, antrum-bearing follicles 72 hours after the first injection (*Evans et al.* 1939). If the thecal "wheel-cells," which are characteristic of hypophyseal deficiency in rats, disappear during the assay, the preparation can be regarded as contaminated with LH.

In *male* hypophysectomized rats (21-day-old at operation, used two days postoperatively) after four daily injections, autopsy on the 5th day reveals a testis enlargement proportionate to the FSH concentration of the preparation. If the preparation is free of LH this is unaccompanied by any stimulation of the accessory sex organs or of the Leydig cells, the enlargement being due exclusively to stimulation of the seminiferous tubules (*Greep et al* 1940). This technic is unreliable in the presence of LH, since the latter also causes some testis enlargement.

Other methods for the bioassay of FSH use intact female rats as test objects and are based upon the AUGMENTATION OF THE OVARY-STIMULATING EFFECT CAUSED BY SIMULTANEOUSLY GIVEN LH, the RAPID STIMULATION OF FOLLICLE MATURATION, the INCREASE IN UTERINE WEIGHT or the PRODUCTION OF CORNIFIED VAGINAL SMEARS. All these technics are less reliable, since compensatory gonadotrophin secretion by the animal's own pituitary tends to blur the picture; indeed the response elicited in some of these tests (e.g., estrus changes) are due to secondary LH-production and not to the injected FSH itself.

Bioassay of the Luteinizing Hormone. — The INTERNATIONAL UNIT (I.U.) of LH is defined as the specific gonadotrophic activity of 100γ of the standard human pregnancy urine preparation kept at the Department of Standards, National Institute of Medical Research, London. It is recommended only for the assay of LH from human pregnancy urine. This I.U. is approximately equivalent to most of the rat units (R.U.) currently in use. Recent progress in the purification of LH will necessitate the establishment of a revised and more generally applicable I.U.

In HYPOPHYSECTOMIZED FEMALE RATS, pure preparations of LH cause restoration of the involuted interstitial cells ("wheel-cells"). Immature rats (26-28-day-old, injections commenced 6-8 days postoperatively) are given three, daily, intraperitoneal injections and are killed 72 hours after the first injection. The minimum amount sufficient to cause just detectable restoration of the "wheel-cells" is considered one unit (*Simpson et al* 1942). It should be kept in mind that the hormone is about five times less active by the subcutaneous than by the intraperitoneal route.

LH can also be assayed in HYPOPHYSECTOMIZED MALE RATS (21-day-old at operation, injections commencing 2 days postoperatively), given 4, daily, subcutaneous injections with autopsy on the 5th day. In this test the increase in the weight of the *ventral prostate* acts as an indicator of activity. The unit is defined as the dose necessary to cause a 100% increase in prostatic weight, as compared with untreated controls (*Greep et al.* 1941). The sensitivity of the method can be increased by intraperitoneal administration of the hormone. This technic has the advantage that FSH does not potentiate the above-

erous factors (body weight, breed, season, light, temperature, etc.) influence the sensitivity of the experimental animals. Subcutaneous injections are most effective and intraperitoneal administration is least efficacious.

(2) The MINIMUM CROP-SAC-STIMULATION METHOD is based upon the fact that minute doses of luteotrophin cause definite crop-gland proliferation detectable if the dissected glands are examined against light (*McShane and Turner*, 1936). The pigeon unit is defined as "the total amount of hormone injected during a period of 4 days, which causes a minimal, but definite proliferation of the crop-glands of 50±11% in 20 common pigeons weighing 300±40 gm." *Li* (1947) uses Silver King pigeons, 4 to 5 weeks of age and weighing 400-550 gm., which are injected subcutaneously once daily for 4 days, with 0.5 cc. of the hormone-containing solution. 24 hours after the last injection, the crop-gland is dissected and examined against light for a positive reaction The unit is defined as the minimum amount necessary to produce a positive response in two out of three birds. Three birds per group are reported to suffice for an assay.

(3) The LOCAL INTRADERMAL CROP-SAC TEST OR MICRO METHOD (*Lyons and Page*, 1935) is so sensitive that it detects 1/10,000 of a unit as determined by the "minimum crop-sac-stimulation test" The hormone solution (0.1 cc.) is injected intradermally into the skin covering one of the crop-sacs on 4 consecutive days. On the 5th day, the birds are killed and the crop-sacs dissected, stimulation being estimated by comparing the transparency to light of the crop-sac on the injected side with the contralateral one

(4) OTHER TECHNICS are based upon the milk *secretion-stimulating-action* of luteotrophin in the suitably pretreated rat or guinea pig, or its *ability to maintain a functional corpus luteum* in hypophysectomized animals. These methods are less accurate and more complicated than the pigeon tests, mentioned above.

Bioassay of Corticotrophin. — No INTERNATIONAL UNIT of corticotrophic activity has as yet been accepted.

(1) The REPAIR TEST (*Simpson et al.* 1943; *Sayers et al.* 1943) is usually performed on 26-28-day-old hypophysectomized *female* rats, which are used 14 days postoperatively when the adrenals have already undergone pronounced involution. The hormone is administered once daily on 4 consecutive days and the animals are sacrificed 96 hours after the first injection. The adrenals are fixed in formalin and frozen sections are stained with Sudan Orange. The lowest dose which causes recognizable REDISTRIBUTION OF THE CORTICAL LIPIDS is considered as the unit; the adrenal weight is not significantly increased even after 100 such units, hence the histologic control is far more sensitive than that based on a weight increase.

(2) The MAINTENANCE TEST (*Simpson et al.* 1943) is based upon the *ability of corticotrophic preparations to maintain the weight of the adrenals* in animals in which injections are commenced immediately after hypophysectomy. 40-day-old male rats are hypophysectomized and injected intraperitoneally once daily during two weeks. By the end of this period, the adrenals of non-treated hypophysectomized rats have regressed from the normal average of 26 mg. to a constant weight of approximately 12 mg. The amount of corticotrophin necessary to maintain the adrenals at the 26 mg. level is defined as one "Maintenance Unit." The sensitivity of this test is greatly augmented if the daily dose is divided into 2 or more injections Since the strain and body-weight of the test rats influences sensitivity, it is well to compare the results with those obtained using a standard preparation under the same conditions and to express the adrenal

total dose of 4 cc. of pregnancy urine is given to prepubertal rats subcutaneously in two injections of 2 cc., at an interval of one hour. If the test is read two hours after the injection, it is extremely unreliable, but after six hours, it gives positive results during gestation in 92.2% of the cases, and after 24 hours, in 100% of the cases. False positives in non-pregnant women are usually due to LH-producing tumors. Even readings after two hours are reliable, if the test is positive.

(3) The FRIEDMAN TEST (1929) is also rapid and simple. It is performed on adult female rabbits, which have been isolated from the male for at least three weeks prior to the test (in order to avoid pseudopregnancy). The morning urine is filtered and 10 cc. of it are injected into the marginal vein of an ear. For preservation, two drops of cresol are added to each ounce of the remaining urine and the specimen is kept in a refrigerator for 24 hours, when a second similar injection is made. 48 hours after the first injection, the rabbit is killed and the ovaries are examined. The macroscopically detectable hemorrhagic follicles are indicative of a positive pregnancy test.

If the urine proves to be toxic, 30 cc. of filtered urine are shaken for 3-5 minutes, with 90 cc of ether. The excess is poured off and the residual ether is removed from the urine by an electric fan. 0.9 gm. of glucose is added to the remnant and then this detoxified specimen is injected in the usual manner. This test gives very reliable results, but only animals weighing more than 800 gm. can be used and the necessity for maintaining a stock of isolated females renders the assay somewhat tedious.

(4) The XENOPUS TEST (*Shapiro and Zwarenstein*, 1933; *Weisman* et al 1942, etc) is based upon the fact that following injection of detoxified pregnancy-urine extracts into the dorsal lymph-sac of female, South-African, clawed frogs (Xenopus laevis), extrusion of ova occurs within 24 hours The eggs are readily detected either in the water in which the animals lay, or following autopsy, within the oviducts This test is alleged to give 98.6% correct results in the diagnosis of pregnancy. At present, in most countries, the difficulty of obtaining these frogs interferes with the general applicability of this, apparently highly satisfactory test.

(5) The FROG TEST (*Galli-Maini*, 1947) takes as a criterion the extrusion of spermatozoa by the male frog, which is readily elicited by pregnancy urine. It appears to be a simple and reliable technic.

(6) A number of OTHER TESTS have been developed in which chemical purification of the gonadotrophins permits the administration of amounts which would not be tolerated by experimental animals, if the original body fluids were injected as such The biologic assay of the concentrates is otherwise essentially the same as in the previously-mentioned tests

Bioassay of Luteotrophin. — The INTERNATIONAL UNIT (I.U) of luteotrophin (prolactin) has been defined as the specific activity contained in 100γ of a standard preparation, made from anterior-pituitary tissue and kept at the Department of Biological Standards, National Institute for Medical Research, London. The use of this unit was recommended "for recording the activity of all crop-gland stimulating preparations."

(1) The CROP-SAC-WEIGHT METHOD (*Riddle et al* 1933) is based upon the observation that the combined weight of the two excised crop-sacs of pigeons is proportional to the amount of luteotrophin injected 6-10-week-old pigeons are injected intramuscularly once daily on 4 days and autopsied about 96 hours after the first injection Under these conditions, the weight of the crop sacs is a linear function of the log of the dose administered It is advisable always to compare results with those obtained under equal conditions with the standard preparation, since num-

5.4±0.26 mg.) in the thyroid weight of 20 chicks whose body weight averages 55±10 gm.

Since the thyroid is not as sensitive to the effect of non-specific damaging agents as the adrenal cortex, it is not always necessary to perform thyrotrophin assays on hypophysectomized animals. Nevertheless, in view of the great sensitivity of the gland to certain dietary constituents, it is well to keep the test animals on "resting diets." Some authors even recommend pretreatment with iodine or diiodotyrosine before the test, to assure that the gland shows no signs of excess activity before the injections are started. The rationale of this procedure is open to question however, since iodine compounds diminish the responsiveness of the thyroid to thyrotrophin and thus decrease the sensitivity of the test.

(4) Various OTHER TESTS are based upon the decrease in the *iodine content of the thyroid* induced by thyrotrophin in the rat or guinea pig; the *restoration of the atrophic thyroid epithelium in the hypophysectomized* rat or pigeon, the *stimulation of the thyroid in the intact grass snake* (tropidonotus natrix), in which the gland is continuously in the resting condition, unless stimulated by exogenous thyrotrophin, etc.

Bioassay of Somatotrophin. — An INTERNATIONAL UNIT of somatotrophin activity has not yet been established.

(1) The BODY GROWTH IN NORMAL INTACT FEMALE RATS about 5-6 months of age and weighing 220-280 gm is a good indicator of somatotrophin activity, since such animals are "plateaued," that is to say, their spontaneous growth rate is practically at a standstill (*Evans and Simpson*, 1931) Usually the hormone preparation is injected daily, intraperitoneally or subcutaneously, in a group of at least 10 normal "plateaued" female rats for 20 days The dose which causes an increase in body weight of 40-60 gm during this period, lends itself best for such assays. The unit is defined as the daily dose required to produce a total body weight increase of 40 gm. in 20 days Since the slope of the growth line increases towards the end of the injection period, a shorter course of injections is not recommended.

(2) The BODY GROWTH OF HYPOPHYSECTOMIZED FEMALE RATS is a more sensitive test-object for somatotrophin Since the weight, age, sex, strain and general condition of the animals influence the results obtained, it is best to use a standard preparation for comparison under identical experimental conditions. Only animals in which the completeness of the hypophysectomy is established by such criteria as cessation of growth, decreased muscular tonus, and maintenance of the fluffy infantile lanugo fur, should be used for the test; the sella must be carefully examined at autopsy, in order to eliminate animals with remnants of anterior-lobe tissue. A unit is defined as the daily dose which causes an average weight gain of 10 gm. in a group of 10 hypophysectomized female rats, 28-30 days of age at operation, and used 10-14 days postoperatively, at which time a course of 9 daily, intraperitoneal injections is commenced and the animals are sacrificed on the 10th day. For greater accuracy, a 15-day injection period is recommended A straight line is obtained if the gain in weight is plotted against the log of the dose given Animals should not be used for such tests more than once since some adaptation (anti-hormone formation [7]) to somatotrophin occurs in time

(3) HISTOLOGIC CHANGES IN THE BONES (e g , TIBIA) OF HYPOPHYSECTOMIZED RATS likewise furnish a useful basis for bioassay purposes. (*Freud et al.* 1939, *Ray et al* 1941, *Evans et al* 1943). 26-28-day-old hypophysectomized female rats are used for the test 12-13 days postoperatively; the hormone is administered intraperitoneally, once daily on 4 successive days.

weight increase per 100 gm. of body-weight.

(3) OTHER METHODS OF ASSAY are based upon the *weight increase produced by corticotrophin in the remaining adrenal of a hypophysectomized animal*, whose other adrenal was removed after hypophysectomy had caused significant involution. The effect of corticotrophin on the *ascorbic acid or cholesterol content of the adrenals* may also be used as an indicator of activity in hypophysectomized rats.

The assay of corticotrophic preparations in intact animals is not to be recommended, since numerous toxic extracts cause a discharge of corticotrophin from the animal's own pituitary, due to the resulting general-adaptation-syndrome. The activity of such endogenous corticotrophins can naturally not be differentiated from that of the injected hormone and this seriously interferes with accurate bioassay. There are no generally accepted methods for the assay of gluco-corticotrophic, mineralo-corticotrophic and other possible specific stimulants regulating the selective production of certain steroids by the adrenal.

Bioassay of Thyrotrophin. — The INTERNATIONAL UNIT (I.U.) of thyrotrophin has been defined as the specific thyrotrophic activity, equivalent to 250γ of a standard pituitary preparation, kept at the Department of Biological Standards, National Institute for Medical Research, London. The third International Conference on the Standardization of Hormones (1938) agreed that only those tests can be considered as safe, which are based on the actual observation of thyroid stimulation, since other, indirect effects may be due to non-specific impurities.

(1) In the RAT (*Anderson and Collip*, 1934) thyrotrophic hormone can be assayed on the basis of the increase in B.M.R. or the histologically-detectable thyroid stimulation which it produces when given after hypophysectomy. In view of the fact that pituitary principles other than the thyrotrophic hormone may also raise the B.M.R., the latter indicator is more reliable.

(2) The GUINEA-PIG is the most commonly employed test-object for thyrotrophin, because of its great sensitivity to the hormone. *Rowlands and Parkes* (1934) adopted as a unit "the thyrotrophic activity contained in an amount of extract which, given daily for 5 days, will cause the thyroid of the 200 gm guinea pig to attain a weight of 600 mg., i.e., about double the normal." Essentially similar assay technics are used by several investigators, although some prefer to measure the average height of the follicular epithelium rather than the weight of the gland.

Heyl and Laqueur (1935) worked out a scale of 6 different stages based on histologic signs of activity; they designated these by the letters p-u. A "border-line dose" is defined as the amount, which given in two intraperitoneal injections on two consecutive days, will cause (within 48 hours) in 2/3 of the treated 150-200 gm. guinea-pigs a reaction "s" in the middle-part of the thyroid. This reaction "s" consists of a thickening of the cells in which the nucleus became round and the cytoplasm developed on the distal cell-pole equals the diameter of the nucleus. In order to keep this unit as close as possible to those generally in use, one "cavia unit" is defined as 1/4 of the "border-line-dose."

Several modifications of these tests are in common use at present.

(3) IMMATURE CHICKS are also very sensitive to thyrotrophin (*Stimmel et al.* 1936; *Smelser*, 1937). *Bergman* and *Turner* (1939) employed the one-day-old white Leghorn chick, emphasizing that males are more sensitive than females. They defined the unit of thyrotrophic activity as the total amount of hormone administered subcutaneously once daily during 4 days, causing a mean increase of 50% (about

(3) Among OTHER BIOASSAY technics, the melanophore-dispersing action in hypophysectomized reptiles (anolis) *Kleinholz and Rahn* (1940), or the erythrophore-dispersing action in fish (phoxinus) *Zondek and Krohn* (1932) have also been recommended. Some investigators believe, however, that the latter test is not specific, because the erythrophores respond to a hormone different from that influencing the melanophores.

Bioassay of Vasopressin. — There are no generally accepted convenient and reliable methods for the bioassay of vasopressin. The official (U.S. Pharmacopeia) posterior-lobe preparations are standardized by their oxytocic potency, which, in most commercially available extracts, runs roughly parallel with the vasopressor activity. Unofficial preparations are available, however, which contain the vasopressor principle in a highly purified state. These are usually assayed for their pressor activity in anesthetized dogs, one unit of pressor action representing that exhibited by 0.5 mg. of the U.S.P. XIII reference standard powder (see: "Bioassay of Oxytocin," below).

Bioassay of Oxytocin.— The most generally accepted tests for the bioassay of oxytocin are based on a comparison of the unknown preparations with the U S P. XIII POSTERIOR-PITUITARY REFERENCE STANDARD. 0.5 mg of this powder is defined as 1 U.S.P. POSTERIOR-PITUITARY UNIT. According to the prescriptions of the U.S. Pharmacopeia XIII, "Posterior-Pituitary Injection" is a sterile, aqueous solution of the water-soluble principles from the posterior-lobe of the pituitary of healthy domestic animals used for food by man. The pituitary must be removed immediately after killing the animals, then dried and either extracted at once or kept in a frozen state until extracted The potency of Posterior-Pituitary Injection must be 1 U S P. posterior-pituitary unit per 0.1 cc. The U.S P. reference standard is prepared under the supervision of the U.S. Pharmacopeia Committee of Revision and is distributed through the office of the Chairman.

Oxytocin is usually assayed on the GUINEA PIG uterus (U.S.P. XIII). The test-animals must weigh 175-350 gm. and should neither have been pregnant nor be in heat. After killing the animal (by a blow on the head or decapitation), the uterus is immediately dissected and one horn is suspended in a bath containing not less than 100 cc. of oxygenated Locke-Ringer solution and kept at a temperature of 37-38°C. One end of the uterine horn is attached to the muscle lever of a suitable kymograph and the assay is commenced 15-30 minutes later, when the uterus is completely relaxed. Appropriate quantities of the preparation to be assayed and of the reference standard are weighed and diluted with isotonic NaCl solution. First, one determines the quantity of the diluted standard-solution and of the preparation to be assayed, which, when alternately administered, elicit a series of four, approximately equally intense, contractions; two with the standard and two with the unknown. After this, a third dose of the diluted standard-solution is given, which is 25% larger than the two preceding doses of the standard. The height of each of 5 contractions is measured. The first four contractions are considered submaximal and equivalent; they constitute an adequate assay, if the difference in height between the highest and lowest of these four contractions is less than half the difference in height, between the lowest of the four and that elicited by the increased dose of the standard. The potency is calculated from the quantities required to produce the four equivalent contractions and is expressed in U.S.P. Posterior-Pituitary Units — Because of the inherent errors of the method, assays 20% above or below the potency of the

Autopsy is performed 24 hours after the last injection and the right tibia of each animal is dissected, split with a razor blade and fixed in neutral formalin. The calcified part of the bone is stained with $AgNO_3$ and $Na_2S_2O_3$. The uncalcified portion of the epiphysis can then be measured under the microscope with a calibrated eye-piece micrometer. The width of the uncalcified cartilage, plotted against the log of the dose of hormone injected, gives a straight line relationship. The test is based upon the fact that after hypophysectomy, the width of the epiphyseal cartilage-plate decreases rapidly, although cartilaginous growth and bone formation may continue for a short time in young animals. This decrease in thickness is due to a disturbance in the normal equilibrium between cartilage and bone formation. Administration of somatotrophin rapidly restores the thickness of the epiphyseal cartilage plate by first stimulating chondrogenesis and then osteogenesis, until the normal equilibrium is re-established. This test is approximately 3 times as sensitive as that based upon body growth.

Bioassay of Other Hypophyseal Hormones. — No generally accepted bioassay procedures have as yet been devised for the estimation of other possible anterior-lobe hormones. This is not unexpected, since the very existence of additional anterior-pituitary hormones is still in doubt The divers actions of impure anterior-hypophyseal extracts are customarily studied under the optimum conditions for the manifestation of their effects, (see above: Classification and Chemistry of the Hypophyseal Hormones). Thus the nephrosclerosis-producing action of anterior-lobe extracts is best demonstrated on unilaterally nephrectomized rats, maintained on a high-sodium and high-protein diet; the diabetogenic action by the resulting destruction of the Langerhans islets, or the hyperglycemia and glycosuria in the dog or partially pancreatectomized rat, etc.

Bioassay of Intermedin. — (1) In the HYPOPHYSECTOMIZED FROG (Rana pipiens) weighing 30-40 gm. (*Teague*, 1939; *Calloway et al.* 1942) the potency of intermedin may be assayed about 24 hours after the operation, when melanophore contraction becomes maximal. The same animals may be used repeatedly so long as 24 hours elapse between complete contraction of the melanophores and re-injection. Injections are made into the ventral lymph sac, through the floor of the mouth It is important to control the pH of the injected specimen and always to compare results with those given by a known specimen at the same pH and at the same temperature. Reading is done under a binocular dissecting microscope, using as a criterium of activity the length of time required for the melanophores to return to full contraction after injection. A minimum of six animals should be used for each unknown and six for the reference standard. The melanophore-hormone unit is defined as the activity equivalent to that of one γ of alkali-treated U.S.P XIII Posterior-Pituitary Reference Standard.

(2) In the SOUTH AFRICAN CLAWED FROG (Xenopus laevis), intermedin may be determined with a probable error of about 10% (*Langrebe and Waring*, 1941). The maximum melanophore contraction attained after injections of extracts into the dorsal lymph-sacs of fully blanched intact or hypophysectomized animals is used as an indicator. In the intact frog, depigmentation is achieved by keeping the animals on a white background

It has been suggested that the *international unit* of melanophore activity in this test be defined as the amount contained in 0.5 mg of the international standard powder. However, this international unit has not yet been officially accepted.

hormone formation in case of intraperitoneal injection ?).

Various hormones of the pituitary have been proven to act directly upon their target organs, following topical application Thus, for instance LH acts directly upon the OVARY, since in the rabbit, injections into individual mature follicles can cause their selective luteinization while the untreated follicles remain unchanged. In amphibia, gonadotrophin treatment of the isolated ovary can even elicit ovulation in vitro

Prolactin stimulates the CROP-GLAND of the pigeon directly, as indicated by the high activity of local administration (see : Bioassays, pp. 222, 223).

Thyrotrophin acts even when directly applied to the THYROID, a fact which can be demonstrated *in vitro*. However, this route of administration is not clinically applicable.

It is highly probable that other trophic actions upon endocrine glands, e.g., that of corticotrophin on the ADRENAL CORTEX and that of the gonadotrophins on the TESTIS, are likewise direct, but this has not yet been clearly proven by experimentation

Intermedin has a direct effect upon CHROMATOPHORES in poikilothermic animals as shown by its local application to certain areas of the skin. This hormone has no clear-cut clinical indication as yet, although it has been claimed to be effective in certain cutaneous pigment anomalies (vitiligo, etc.).

Both posterior-pituitary principles are usually administered by the subcutaneous or intramuscular route, although they are also absorbed from MUCOUS SURFACES (e.g , vagina, nose, etc).

Since oxytocin causes contractions of the UTERUS and vasopressin contractions of ARTERIAL SEGMENTS in vitro, it is evident that both these principles act directly upon their respective peripheral target-organ

LH is readily absorbed by the TRANSPLACENTAL ROUTE as shown by the high LH concentration of the blood and urine in women during pregnancy.

SENSITIZATION AND DESENSITIZATION

Anterior-Pituitary Hormones. — There is no clear-cut evidence showing that upon continued administration true sensitization to ANTERIOR-PITUITARY HORMONES can occur. On the contrary — probably as a result of antihormone formation — chronic treatment with FSH, LH, prolactin, somatotrophin, thyrotrophin and corticotrophin causes a considerable degree of desensitization, often culminating in complete lack of responsiveness (see : Antihormones).

Intermedin.— Upon continued treatment with intermedin, the organism does not become abnormally sensitive or resistant to it, as long as a period of about one day is allowed between two injections.

Posterior-Lobe Hormones. — Oxytocin and vasopressin likewise fail to cause resistance, as a result of chronic pretreatment. However, if two injections of the vasopressin are administered in rapid succession, the second dose often proves inactive or at least less active. This phenomenon has variously been referred to as "tachyphylaxis" or "skeptophylaxis."

ACTIVATION AND INACTIVATION

FSH and LH. — The fact that LH AND FSH MUTUALLY ACTIVATE EACH OTHER, in the sense of a synergistic (potentiating) effect, has already been mentioned.

Prolonged *treatment* with FOLLICULOIDS (resulting in ovarian atrophy) slightly counteracts the action of FSH or LH, but apparently only because the ovary is subnormal in size at the onset. Conversely, sudden heavy overdosage with folliculoids (presumably through peripheral synergism with circulating hypophyseal luteotrophin) tends to increase the efficacy of FSH and LH preparations in intact animals, inasmuch as it permits the formation of the large pregnancy-type corpora lutea

A number of protein-precipitants and other AGENTS CAUSING LOCAL IRRITA-

standard are generally considered acceptable.

Several OTHER METHODS for the *bioassay of oxytocin have been recommended, but none of these are commonly in use.*

MODE OF ADMINISTRATION

None of the pituitary hormones are active when given by the ORAL route, presumably because these proteins and polypeptides are hydrolyzed by the *gastrointestinal enzymes.*

All hypophyseal hormones are usually administered SUBCUTANEOUSLY or INTRAMUSCULARLY. Chemically pure anterior-pituitary preparations are not yet commercially available. They are usually distributed in the form of partially purified extracts in aqueous solution, the potency being expressed in various biologic units. Highly purified *LH (from human pregnancy urine, human placenta or animal pituitaries) are available in ampules containing 100 to 5,000* I.U./cc. *FSH* (from pregnant mare *serum) or mixtures of* FSH *and* LH (since the two hormones mutually *potentiate each other),* as well as aqueous solutions of *luteotrophin, thyrotrophin, somatotrophin and corticotrophin* are distributed in ampules. Their potency is also expressed in various biologic units.

Clinical experience with these extracts does not yet warrant detailed discussion of recommendable doses. Meanwhile, in determining the optimum dose for any one case, the physician must largely depend upon trial and error, relying partly upon the recommendations of the pharmaceutic companies which distribute these preparations.

The use of luteotrophin (prolactin) *has been recommended to increase sub*normal milk secretion, but so far, results *in lactating* women are not particularly striking.

Somatotrophin is used in the treatment of dwarfism, especially the type due to anterior-lobe failure. However, the danger of causing premature closure of the epiphyses must be kept in mind.

Thyrotrophin is recommended for the treatment of hypothyroidism, especially that due to pituitary failure.

Corticotrophin would appear to be the logical therapy of hypocorticoidism, *especially in* cases of anterior-pituitary failure, but at present, an adequate sup*ply of potent corticotrophin is not yet* commercially available.

Other anterior-lobe principles and intermedin are not yet used in clinical medicine.

The usual commercial *posterior-pituitary preparations are the* U.S.P. Posterior Pituitary Solution, standardized to contain one U.S.P. Posterior-Pituitary Unit/0.1 cc. Pituitrin (N.N. R.) is merely a brand of posterior-pituitary solution. U.S.P. pitressin (N.N.R.) contains 10 units of pressor activity and less than one unit of oxytocic potency per cc, while pitocin (N.N.R.) contains 10 units of oxytocic activity and less than 0.5 unit of pressor potency.

It is customary to distinguish the so-called "surgical" *posterior-pituitary so*lution, which possesses twice the poten*cy of the official Posterior-Pituitary So*lution, from "obstetrical" Posterior-Pituitary Solutions which are of stand*ard strength* (1 unit/0.1 cc).

LH is considerably more active when given INTRAPERITONEALLY than by the subcutaneous or intramuscular route, a fact which has already been mentioned in connection with its application to bioassays. — It is noteworthy, however, that the gonadotrophic effect of *crude anterior-pituitary preparations is* much more pronounced following sub*cutaneous than after intraperitoneal* injection In fact when given intraperitoneally they may even inhibit the gonad-stimulating effect of simultaneously, subcutaneously injected LH. — The mechanism of this action is not yet clear (greater intraperitoneal activity of contaminating *anti-gonadotrophic* substances? Greater endogenous anti-

of the thyroid (e.g., exophthalmos), but the experiments upon which this conclusion was based will have to be repeated with entirely pure hormone preparations. There is no evidence to indicate that FSH, LH or corticotrophin exert any direct effect upon tissues other than the receptive cells in the gonads and adrenal cortex respectively.

The available data concerning the actions of impure anterior-hypophyseal extracts upon the pancreas, kidney, thymus, metabolism, etc., are not sufficient to express any opinion concerning the underlying mechanism of action.

Different Kinds of Hypophyseal Hormones. — Unlike in other sections of this book, the possibility of additional, hitherto unproven, hormones of the hypophysis will not be considered here, since it has been discussed previously under the heading : "Classification and Chemistry of the Hypophyseal Hormones," (see : pp. 210-214).

EXPERIMENTAL PHYSIOLOGY OF THE HYPOPHYSIS

EXPLANTATION OF THE HYPOPHYSIS

The anterior-lobe of various animal species grows quite well in TISSUE CULTURE. The hypophyses of lower vertebrates lend themselves better to this type of experiment than those of the higher mammals, but rat and guinea-pig anterior-lobe tissue can also be maintained and may even proliferate in vitro. Parker's method (which involves the use of a fluid medium and a high oxygen tension) is especially recommended. Posterior-lobe tissue, on the other hand, is singularly unsuited for in vitro cultures.

ORGAN CULTURES of anterior-lobe tissue are rarely successful, because of the complex blood-vessel system, which does not lend itself well to perfusion with a pump. However, for many types of experiments it suffices to isolate and perfuse the entire head (e.g., of a dog), comparing the composition (e.g., hormone concentration) of the perfusion fluid before and after removal of the hypophysis from the preparation

TRANSPLANTATION OF THE HYPOPHYSIS

Anterior-lobe tissue and to some extent, even intermediate-lobe tissue lends itself to grafting. Autotransplantation and to a lesser extent, homotransplantation of anterior-lobe tissue is often successful, but heterotransplantation has never been proven to give permanently surviving grafts.

TECHNIC OF HYPOPHYSECTOMY

The technic of hypophysectomy is different in the various species, depending mainly upon the anatomic configuration of the skull and the sella turcica Since this is a rather delicate intervention frequently used in endocrine research we shall describe it in some detail.

It is especially simple in AMPHIBIA. In the frog, for instance, it suffices to tie the animal to a board on its back and then, under ether anesthesia, the mucosa can be incised along the midline of the palate, so as to expose the parasphenoid. The mouth is washed with an antiseptic solution and, with a dental burr, a hole is made at the place where the median line crosses a transverse line which goes through the lateral processes of the parasphenoid. The hole should not go all the way through to the pituitary, the last remnant of cartilage being removed with a cataract-needle. After this, the hypophysis is extracted by suction through a glass pipette.

In the anura, permanent contraction of the chromatophores (due to lack of intermedin) and great muscular weakness are the most oustanding characteristics of hypophyseal deficiency.

In BIRDS, either the trans-buccal or the trans-orbital approach may be used. Since the orbits of birds are very large, and separated from the hypophysis merely by a thin membrane of bone, it

TION (e g , salts of mercury or zinc, urine extracts, various proteins, trypan blue, tannic acid, etc.) also tend to augment the action of FSH and LH, but this is probably only due to a delay in their absorption rate. The effect is somewhat comparable to the augmentation of effect obtainable when steroid hormones are given as their esters or as crystal pellets, rather than as readily absorbable, oily solution of the free compounds. This interpretation is based mainly upon the fact that when the gonadotrophin and the irritating substances are injected at different sites, the latter exert no potentiating action.

Luteotrophin. — The effect of luteotrophin upon the ovary — unlike that upon milk secretion — is greatly augmented by folliculoids. This is apparently due to a peripheral synergism since the production, by impure anterior-pituitary extracts, of pregnancy type corpora lutea, is enhanced by folliculoids even in the hypophysectomized rat.

Intermedin and the Posterior-Lobe Hormones. — There are no noteworthy data concerning the activation and inactivation of INTERMEDIN, except its activation (in vitro) by alkali (p. 218).

The actions of OXYTOCIN and VASOPRESSIN are not significantly influenced by simultaneous treatment with other drugs. However, substances which delay the absorption (e g , tannic acid) of these hormones tend to increase and prolong their effect, while conjoint treatment with oxytocin and other oxytocics or vasopressin and other vasopressor substances may lead to the phenomena of synergism

THEORIES CONCERNING THE HYPOPHYSEAL HORMONES

Biogenesis and Metabolism of the Hypophyseal Hormones. — There are no reliable data concerning the PRECURSORS from which the various hypophyseal hormones are synthesized in the body. It is evident, however, that the molecules of these protein-hormones must be made from the constituent amino-acids or polypeptides.

The fate of the anterior-lobe hormones, and the pathways through which they are metabolized, are likewise incompletely understood. HEPATIC DETOXIFICATION does not appear to play an important rôle in the inactivation of any hypophyseal hormone. If very large quantities are administered, or endogenously produced, they tend to be ELIMINATED IN THE URINE; presumably because of their comparatively low molecular weight. This is particularly obvious in the case of the gonadotrophins FSH and LH, of which very large quantities are excreted in the urine, especially during pregnancy and following gonadectomy. Traces of the anterior-lobe hormones, as well as intermedin and the posterior-lobe hormones, have likewise been claimed to be demonstrable in the urine, but only on the basis of indirect evidence.

As outlined in the Introduction, hormones are not likely to be "UTILIZED" by their respective target organs while they exert their effects. This has been shown in an especially convincing manner for the gonadotrophic, thyrotrophic and corticotrophic hormones whose activity appears to be entirely independent of the amount of receptive (target organ) tissue present in the organism.

Mechanism of Hypophyseal Hormone Actions. — FSH, LH, luteotrophin, corticotrophin, thyrotrophin, somatotrophin, intermedin, vasopressin and oxytocin are all believed to act directly upon their respective target organs as judged by the results of topical application in vitro and in vivo (See: Mode of Admin. pp. 228-229.) The intimate mechanism through which they influence the receptive cells is not known, but it is probable that they act through their effect upon the enzyme mechanisms regulating organ growth and function.

It has been claimed that thyrotrophin has certain actions even in the absence

fastened to a board on its back and placed on a narrow table. The operator sits near the tail, the assistant, near the head end of the animal. A longitudinal incision of about 2 cm. is made from the submental papilla downwards.

(2) The operator introduces two bent forceps just below the thyroid artery, to the spheno-occipital synchondrosis. Since this artery is much more caudally situated than the synchondrosis, the direction in which one has to advance the forceps is at the same time ventro-dorsal and caudo-cranial. If this approach is used, it is not necessary to cut the digastric or any other muscle, since one can advance all the way through in the intermuscular spaces. When the forceps touch the sphenoid, they are handed over to the assistant without moving their tips. These forceps keep soft tissues out of the way and expose the sphenoid bone. If a cannula has been inserted into the trachea (to facilitate respiration), the forceps need not be moved until the end of the operation. With some practice, it is possible, however, to perform the operation without the use of a tracheal cannula. In this event, the forceps compressing the trachea have to be removed from time to time in order to allow the animal to breathe. Since a great deal of practice is needed to perform the operation in the latter way, beginners are advised to use the tracheal-cannula-method.

(3) After the sphenoid is exposed, the bone is cleaned, rostrad from the synchondrosis, with the help of a piece of cotton pushed with the end of a hard probe

(4) In animals weighing 100 gm. or more, the bone is perforated by means of a No 10 dental burr. For smaller animals, smaller burrs are used.

(5) After the bone has been removed, the dura is torn with the help of a small dental pick and the gland is aspirated It usually comes out in one piece, if the suction is applied very gently at first, so as to lift the hypophysis out of its normal position before removing it with strong suction. If the gland should break, one may remove the remainder from behind the bone, with the help of the dental pick.

(6) The assistant removes the forceps and the skin is sutured.

Since the intervention should not take more than three minutes, it suffices to have the animal well anesthetized at the beginning of the operation. If the tracheal cannula plugs up with mucus and the animal becomes asphyctic, one may apply artificial respiration through the cannula itself. The width of this tube should not exceed 1/4 of the width of the trachea

With but minor modifications, to adjust the operation to the varying anatomy of the skull, this same approach is recommended for hypophysectomy in the GUINEA PIG, MOUSE, FERRET, HEDGEHOG, and most other mammals with elongated crania.

In MAN, the *transnasal* or *transsphenoidal* approach is usually selected for the removal of pituitary tumors, which tend to grow into the sphenoid towards the nasal cavity. In general, however, the *transfrontal* approach is preferred in human surgery The procedures used by different surgeons vary, but the main feature is to make an osteoplastic flap, so that the frontal lobe, preferably the right, can easily be retracted and the chiasmal region approached. Two types of skin incisions are used, the first runs up from the temporal region along the coronary suture to the midline, then turns down sharply to the root of the nose and after this, turns back along the upper margin of the orbit. This leaves almost no scar as the two parallel incisions, the orbital and the temporal, are covered with the eyebrow and hair respectively The only scar which shows is a straight line running down on the forehead and this is almost invisible, if the edges of the skin wound are carefully adapted A second type of incision follows the parietal suture from one temporal region to the other and the skin flap is reflected towards the

is easy to reach the pituitary after ablation of an eye-ball.

In the DOG, we usually employ the following technic: The dog (preferably a young animal weighing 6-10 Kg.) is tied to the table on his back under *light ether anesthesia. Since hypophysectomy* greatly decreases resistance to injection anesthetics, ether-saturated air is introduced into the trachea through a rubber catheter during the entire intervention

The table is slightly inclined, so that the head is at the lowest level. This prevents aspiration of mucus and blood during the operation. Two vertical steel bars are fastened to that edge of the table where the head lies. Two horizontal cross rods slide up and down along the vertical bars. The two horizontal bars are placed between the teeth of the dog and then separated as far as possible, in order to open the mouth maximally. The prominent canine teeth keep the bars from sliding out of the oral cavity. The whole table is then covered with sterile cloth, leaving only the oral cavity exposed, this is washed with an antiseptic solution (e.g., trypaflavine). A longitudinal incision is made in the midline of the soft-palate, beginning about one cm. behind the caudal margin of the hard-palate and extending 3-4 cm. backwards The wound is opened wide by two lead sutures passed through the palate, one on each side, attached to the vertical bars after maximal lateral traction The posterior wall of the pharynx thus becomes clearly visible when illuminated by a strong beam of light from a lamp attached to the surgeon's forehead Then the pharyngeal mucosa is washed with antiseptic solution.

At this time, the gloves and all instruments are changed, since the first part of the operation is septic. The pharyngeal muco-periosteum is now strongly compressed with a cotton-pad, so as to render it anemic. Then a cross-incision is made, the transverse branch of which is at the level of the two pterygoid processes Along the margins of the incision, the muco-periosteum is now separated and reflected from the bone, thereupon, *in young dogs, the spheno-occipital* synchondrosis becomes visible as a bluish, transverse cartilage line; *in old animals, a transverse crista* may take its place, or it may be entirely absent. Just rostrad from this line, a small emissary vein comes out of the sphenoid and since this bleeds, it serves as a readily detectable landmark, designating the place where the drill hole should be made to gain access to the hypophysis

The drill used should be somewhat smaller than the pituitary itself. As soon as the dura is reached, the circular sinus surrounding the pituitary becomes faintly visible as a blue circle in the middle of which is the pink anterior-hypophysis. The dura is incised longitudinally with a fine lancet, upon which the pituitary protrudes as a result of intracranial pressure. At this point the gland is first loosened by means of a blunt probe and then extracted through a glass cannula which is connected with a suction pump. This is followed by the loss of several cc. of clear cerebro-spinal fluid. To ascertain that no pituitary tissue is left behind, it is advisable to scrape the whole interior of the, now vacant, sella with a small, blunt curette Finally, the pars tuberalis is removed from the stalk with a very fine suction cannula.

It is not necessary to close the drill hole, since soon after operation a clot is formed in the sella and this prevents infection of the meninges The soft palate is closed by two or three stitches and the mouth rinsed with antiseptic solution.

Essentially the same approach may be used for hypophysectomy in the CAT, RABBIT and MONKEY.

In the RAT, as in many other rodents, the para-pharyngeal approach is preferred. The operation is performed as follows:

(1) The ether-anesthetized rat (preferably 40-120 gm. body-weight) is

are ineffective. It is probable, however, that thyrotrophin is not the only anterior-lobe hormone responsible for the maintenance of the normal metabolic rate.

The specific dynamic action of *proteins* is diminished by hypophysectomy and restored to normal by suitable anterior-pituitary extract therapy.

In intact animals, excessive doses of ANTERIOR-LOBE EXTRACTS raise the B. M.R. above normal, again mainly, (but perhaps not exclusively) due to their thyrotrophin content. *Iodides* inhibit the B.M.R. raising effect of thyrotrophin, presumably due to their ability to counteract the action of this hormone upon the thyroid itself.

POSTERIOR-LOBE EXTRACTS likewise tend to raise the B M R. in various animal species including man, vasopressor preparations being generally more active than the oxytocic. Some investigators claim to have prepared a "specific metabolic principle" from the posterior-lobe. It allegedly causes an immediate rise in B.M.R., accompanied by a fall in R.Q., these changes being more rapid than those obtained with other pituitary preparations.

Carbohydrate Metabolism. — (1) BLOOD SUGAR. While the blood sugar of well-fed HYPOPHYSECTOMIZED animals tends to remain within normal limits, fasting or exposure to almost any type of non-specific damage elicits an unusually pronounced, often fatal, hypoglycemia This is generally ascribed to deficient gluconeogenesis, which renders hypophysectomized animals incapable of mobilizing sugar from non-carbohydrate stores.

Gluco-corticoids and *anterior-pituitary extracts* restore the fasting blood sugar to normal, but further work, with highly purified anterior-lobe principles, will have to be performed in order to identify the particular hormone (or hormones) responsible for this effect; *posterior-lobe extracts* are ineffective.

Pancreatectomy fails to elicit the customary marked hyperglycemia and glycosuria, in the absence of the pituitary. Thus, for instance, dogs which have been both hypophysectomized and pancreatectomized ("Houssay dog") develop only a very mild diabetes and may survive almost indefinitely without insulin therapy. Apparently the absence of diabetogenic and metabolism-stimulating (e g., thyrotrophic) anterior-lobe hormones partly compensates for the loss of the Langerhans islets.— (Cf. hexokinose theory, p. 494.)

Conversely, *adrenalectomy* or *insulin* administration, tend to cause a particularly pronounced and rapid hypoglycemia following hypophysectomy. As for the pronounced fasting hypoglycemia, a deficient gluconeogenesis is principally responsible for this reaction.

The hyperglycemic action of *adrenaline* is decreased in hypophysectomized animals, even if the hepatic glycogen stores are adequate. This is not due to a delay in the absorption (diminution of hyperglycemic action manifest even if adrenaline is injected intravenously), nor is it due to increased sugar utilization (intravenous glucose still produces marked hyperglycemia).

After feeding of certain *carbohydrates* (e g., starch), the rise in blood sugar is not quite as marked in hypophysectomized as in intact rats. However, this may be merely due to a decreased intestinal absorption rate. The hyperglycemia caused by intravenous administration of glucose lasts longer in hypophysectomized than in normal animals, perhaps because in the absence of the pituitary, glycogen deposition in the liver is diminished.

After hypophysectomy *phlorhizin* causes hypoglycemia and a subnormal degree of glycosuria. Simple anterior-lobe extracts suffice, however, to normalize the response of hypophysectomized animals to phlorhizin

In intact animals impure ANTERIOR-LOBE EXTRACTS raise the blood sugar It is reasonable to assume that the glycotropic, glycostatic, and diabetogenic actions (see Classification of the

face, so as to expose the frontal and parietal bones. The bone flap is made from these with a temporal basis in the same manner as if the first type of incision had been used. With this technic, no visible scar remains. The operative mortality is about 5%.

EFFECTS OF HYPOPHYSECTOMY AND HYPOPHYSEAL HORMONE TREATMENT

State. — The appearance of experimental animals following HYPOPHYSECTOMY resembles that of hypopituitary patients (see: Hypopituitarism). If the operation is performed early in life, the animals fail to grow and retain their lanugo-like puppy fur. If, on the other hand, the pituitary is removed during later life, the fur is merely scanty. In either case, the muscular tonus and strength are far below normal and the sex organs are deficiently developed.

Resistance to various types of non-specific damaging agents (infections, intoxications, trauma, etc.) is greatly diminished by hypophysectomy, mainly because in the absence of the anterior-lobe, animals are incapable of responding to damage with the normal increase in corticoid hormone secretion.

All these deficiency manifestations can be almost completely eliminated by adequate *anterior-lobe hormone* treatment Resistance to non-specific damage can also be improved by *corticoid* therapy.

Treatment of intact animals with excessive doses of ANTERIOR-LOBE HORMONES rarely produces any acute signs of overdosage, but following several days of treatment the specific biologic effects of the various hormone principles become evident (stimulation of the gonads, thyroid, adrenals, somatic growth, etc.).

INTERMEDIN does not appear to be toxic or to cause any change in the appearance of mammals, although in lower vertebrates, it elicits the well-known changes in skin color. (See: pp. 217 and 243.)

In man, toxic doses of POSTERIOR-LOBE EXTRACTS cause marked pallor of the face as a result of vasoconstriction, but a rise in blood pressure is rarely observed. Stimulation of intestinal motility is likely to elicit nausea, belching, intestinal cramps and a desire to defecate. Women often complain of dysmenorrhea-like uterine cramps Because of possible vascular complications, the use of posterior-pituitary extracts is contraindicated in individuals suffering from cardiovascular and especially coronary disease.

Temperature. — The body temperature of HYPOPHYSECTOMIZED animals is usually slightly below normal. Crude anterior-lobe extracts, thyroxin and corticoids tend to raise it towards normal. However, the hypothalamic centers are much more important for temperature control and incidental lesions of these nuclei may well be responsible for some of the changes observed after hypophysectomy

In intact animals, overdosage with ANTERIOR-LOBE EXTRACTS (unless they contain large amounts of thyrotrophin) rarely causes any significant change in body temperature.

POSTERIOR-LOBE EXTRACTS tend to raise the body temperature, especially in animals whose temperature-regulating mechanism is deranged due to destruction of the thalamus.

Basal Metabolism. — HYPOPHYSECTOMY causes a considerable decrease in the B.M R.; in the rat, for instance, B.M.R. measurements of —45% have been recorded after hypophysectomy.

The rise in B M.R. normally elicited by *pancreatectomy* in the dog is not seen in previously hypophysectomized animals.

Thyroidectomy causes a further decrease in the already low metabolic rate of the hypophysectomized animal.

Anterior-lobe extracts (especially thyrotrophin) and *thyroid hormone* are highly effective in restoring the low B.M.R. of hypophysectomized animals to normal, while *posterior-lobe extracts*

the muscles, retains this effect even after hypophysectomy.

Lipid Metabolism. — HYPOPHYSECTOMY slightly decreases the fatty acid and total lipid concentration of the blood and markedly inhibits the lipemia otherwise produced by pancreatectomy.

The production of fatty livers (by partial hepatectomy and fasting, carbon tetrachloride, phosphorus, etc.) is inhibited by hypophysectomy, but restored following anterior-pituitary extract treatment. Adrenalectomy likewise prevents fat-deposition in the liver under similar conditions, while corticoids restore the ability of adrenalectomized or hypophysectomized animals to develop fatty livers; hence it is highly probable that corticotrophin is important for this response.

The tendency of hypophysectomized animals (especially dogs) to become very adipose is partly due to the polyphagia caused by accompanying hypothalamic lesions and partly to the aversion of these animals to perform muscular exercise. Bilateral lesions, interrupting the nerve fibers which originate from the caudal portion of the paraventricular nuclei and descend to the brain stem, cause polyphagia and adiposity irrespective of the presence or absence of the hypophysis

In intact animals, the changes in blood-lipids obtained with ANTERIOR AND POSTERIOR-LOBE EXTRACTS are rather variable, since no systematic work has been done with purified hormones, they do not deserve a detailed discussion here

It is noteworthy, however, that various impure anterior-lobe extracts cause marked *ketonuria* and *ketonemia*, although the assumption that a special "ketogenic hormone" exists has not been proven. Extensive partial-hepatectomy inhibits the ketogenic effect of anterior-lobe extracts, because the liver is the source of ketone body formation.

Nitrogen Metabolism. — HYPOPHYSECTOMY causes no very specific change in nitrogen metabolism, although protein anabolism is obviously impeded (mainly due to lack of somatotrophin). The fact that fasting hypophysectomized animals tend to eliminate less endogenous nitrogen than normals can be explained by the comparatively low protein reserves of the former.

Phlorhizin causes a less pronounced loss of nitrogen and a lower urinary D/N (dextrose per nitrogen) ratio in hypophysectomized than in normal, or even in thyroidectomized, animals. This may likewise be partly due to subnormal nitrogen reserves and perhaps also to the inhibition of gluconeogenesis from protein during anterior-lobe failure.

ANTERIOR-LOBE EXTRACTS (as well as pure somatotrophin) increase nitrogen anabolism and tissue-growth both in hypophysectomized and in intact animals. POSTERIOR-LOBE HORMONES exert no specific effect upon protein metabolism.

Endogenous *creatinine* excretion and the *phosphocreatine* concentration of the muscles decrease following hypophysectomy, but are restored towards normal by anterior-pituitary extracts. It has been stated that a derangement in creatine metabolism may be partly responsible for the muscular asthenia, so characteristic of anterior-lobe deficiency.

Salt and Water Metabolism. — Hypophysectomy causes transient POLYURIA in most animal species, but this operation in itself does not produce permanent diabetes insipidus. To cause marked, persistent polyuria some anterior-lobe tissue must be preserved and the lesion must either destroy the posterior-lobe or sever the connection between the supraoptic nuclei and the hypophysis, the latter operation is followed by atrophy of the pars nervosa, whose endocrine secretion is apparently under the nervous control of these nuclei. Unlike the permanent phase of diabetes insipidus, the initial, transitory

Hypophyseal Hormones, p. 213) are *responsible for this effect (see also* effect on "Glycogen stores," below). However, only experiments with pure anterior-lobe hormones will permit elucidation of the underlying mechanisms.

While pure INTERMEDIN has no effect on the blood sugar, POSTERIOR-LOBE EXTRACTS *cause marked hyperglycemia,* due to their vasopressin content. However, the blood sugar rise can only be elicited with toxic doses and is accompanied by such marked vasomotor phenomena that it can hardly be regarded as a specific hormone-action. A secondary liberation of adrenaline and the non-specific glycogenolytic effect of such toxic doses suffice to explain the observed results.

(2) GLYCOGEN STORES. The glycogen stores of fed HYPOPHYSECTOMIZED animals remain approximately normal. However, after a comparatively short period of fasting, the liver-glycogen and, to a lesser degree, the muscle-glycogen values decrease much more ra*pidly in the hypophysectomized than in* the intact animal. This has been ascribed to a lack of the "glycostatic factor," since treatment with suitable *anterior-lobe extracts* restores the power of the fasting hypophysectomized animal to maintain its glycogen stores.

Anterior-lobe extracts maintain the muscle-glycogen values of hypophysectomized rats much more readily than the liver-glycogen stores. This effect is manifest even *in adrenalectomized rats* and is not due to corticotrophin Several other observations also support the view that following hypophysectomy, the derangement in glycogen storage is not merely due to a secondary deficiency in gluco-corticoid secretion Thus, hypophysectomized rats are unable to maintain their fasting muscle-glycogen values immediately after the operation, while adrenalectomized animals develop this deficiency only gradually. Furthermore, in adrenalectomized rats, corticoid or salt therapy restores the glycogen values towards normal much more readily than after hypophysectomy. However, large doses of *gluco-corticoids* also tend to replenish the liver and muscle-glycogen stores in hypophysectomized animals. Hence, corticotrophins probably also influence this reaction.

It is noteworthy that although separately both *hypophysectomy* and *pancreatectomy* decrease the muscle and liver-glycogen concentration, this effect is not seen if both glands are removed from the same animal (e.g , dog, cat).

The glycogenolytic effect of *adrenaline is inhibited by hypophysectomy,* but only if the hormone is administered subcutaneously, not in the event of intravenous infusion. It is concluded that the inefficacy of subcutaneously administered adrenaline is merely due to a deficient hormone absorption.

In intact animals (e.g., rabbit, rat), impure ANTERIOR-PITUITARY EXTRACTS increase the liver glycogen stores, while POSTERIOR-LOBE EXTRACTS (especially *vasopressin) deplete them in proportion* to the resulting hyperglycemia.

(3) CARBOHYDRATE ABSORPTION. Following oral administration of glucose, the deposition of liver and muscle glycogen in previously fasted, hypophysectomized rats proceeds at an almost normal rate. Thus there is no evidence of any significant decrease in glucose absorption, although the uptake of complex carbohydrates (e g., *starch) is delayed.*

(4) LACTIC ACID. The blood-lactic-acid content does not show very pronounced variations, either after hypophysectomy or after anterior-pituitary extract treatment

Vasopressin (but not oxytocin) raises the lactic acid content (e.g., dog)

(5) HEXOSEMONOPHOSPHATE. The hexosemonophosphate content of muscles does not show any significant change after hypophysectomy in the rat. Adrenaline, which increases the hexosemonophosphate concentration in

the muscles, retains this effect even after hypophysectomy.

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polyuria is not affected by the NaCl intake or by injection of posterior-pituitary extract; it is abolished by thyroidectomy *and is independent of the presence* of anterior-lobe tissue.

It is now generally accepted that the anti-diuretic action of posterior-pituitary extracts is due to stimulation of the *water re-absorption in the descending* loop of Henle within the kidney. In vitro, in a heart-lung-kidney preparation (dog) there is profuse polyuria which can be inhibited by introducing into the perfusion system a head containing the hypothalamus and hypophysis. No such anti-diuretic effect is achieved by introduction of a head deprived of the hypophyseo-hypothalamic system.

Data indicating that the anti-diuretic hormone is probably identical with vasopressin has been enumerated in the chemical section (See : p. 219.)

Several observations suggest that administration of water inhibits the secretion of anti-diuretic pituitary hormone, while dehydration increases it. Through this mechanism, the posterior-lobe could participate in the normal regulation of diuresis. Nevertheless, even in hypophysectomized animals whose hypothalamus is simultaneously destroyed, the administration of water causes transitory diuresis, indicating that the hypophyseo-hypothalamic mechanism is not the only regulator of this activity.

The polyuria elicited by posterior-lobe destruction precedes the polydipsia and excessive diuresis continues for some time, even if water *is withheld. Furthermore, complete* nephrectomy prevents the abnormally high fluid intake caused by posterior-lobe destruction. Hence, increased urine formation appears to be the primary phenomenon in this type of polyuria.

In amphibia (e.g., frog) posterior-lobe extracts (presumably vasopressin) increase the total water content of the body, primarily due to an increase in the water intake through the skin.

Treatment with impure *anterior-lobe extracts*, corticoids or thyroid hormone increases diuresis even long after complete hypophysectomy.

Administration of *sodium chloride* causes more *pronounced polyuria* in animals with hypothalamic diabetes insipidus than in intact controls.

Normally, water reabsorption (such as is characteristic of the anti-diuretic hormone) is usually enhanced by an increase in the concentration *of serum solutes, perhaps specifically Na (Verney, 1946)*. According to *Peters (1945)* it can also be inferred by the comparison of the two types of experimental diabetes insipidus, as outlined below.

Posterior-lobe destruction	Desoxycorticosterone overdosage
Initial inhibition of water reabsorption Primary diuresis Deficient body water Deficient body Na	Initial increase of Na reabsorption Primary thirst Excess body water Excess body Na

CHLORIDE elimination through the urine is *greatly* diminished in dog kidneys perfused by means of a heart-lung preparation. However, the addition into the circulation of the head of a dog *(containing the pituitary)*, or *addition* of posterior-pituitary extract to the perfusion fluid, results in a decreased diuresis due to better chloride concentration.

Destruction of the posterior-lobe, and to a lesser degree, incomplete hypophysectomy, decreases *both the absolute* amount and especially the concentration of chloride eliminated in the urine; this effect is also prevented by posterior-lobe extract.

In the intact organism, purified vasopressin likewise increases chloride elimination in the urine in spite of its antidiuretic action; oxytocin, however, raises the total Cl output (only due to its diuretic action), without changing the urinary Cl concentration.

Data are somewhat contradictory concerning the serum-chloride concentration after selective removal of the posterior-lobe or complete hypophysectomy; sometimes the serum-chloride level remains normal, while in other instances, hyper- or hypochloremia is observed. For reasons not yet clearly understood, the hypochloremic effect

of desoxycorticosterone acetate is inhibited by hypophysectomy.

The urinary SODIUM elimination tends to run parallel with the chloride excretion following various types of hypophyseal and hypothalamic lesions. The blood sodium concentration shows less consistent changes.

POTASSIUM and CALCIUM metabolism are not very significantly influenced by hypophysectomy or the administration of pituitary extracts. It is noteworthy, however, that hypokalemia (similar to that produced with desoxycorticosterone) can be elicited with certain corticotrophic anterior-lobe extracts.

The inorganic PHOSPHATE content of the blood and muscles tends to decrease after hypophysectomy in several animal species, and can be restored towards normal by treatment with crude anterior-lobe extracts. Excessive doses of such preparations may even raise the serum-phosphate concentration above normal.

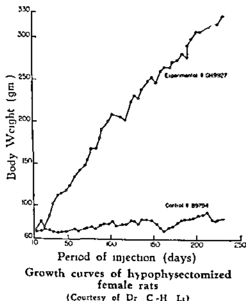
Both anterior and posterior-lobe extracts counteract the hypophosphatemia normally elicited by insulin or glucose administration.

Hypophysectomy decreases the blood IODINE concentration while subsequent treatment with thyrotrophin raises it to or even above normal. This reaction is apparently mediated by the thyroid, since it does not occur following thyroidectomy.

Other Metabolites. — The decrease in metabolism and growth-rate occasioned by hypophysectomy and the stimulation of these processes by anterior-pituitary extracts, produces secondary changes in the requirements of the body for essential amino-acids, vitamins, minerals, etc. However, neither hypophysectomy nor administration of pituitary extracts has been shown to have any consistent and significant specific effect upon the metabolism of other body constituents.

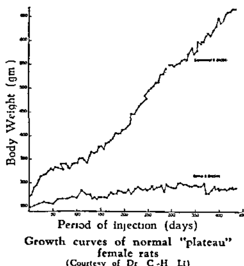
Growth and Bone Structure. — In all mammals and even in most other vertebrates, hypophysectomy causes an immediate cessation of growth in length, except during embryonic and very early (first few weeks) postnatal life. Curiously, in certain lower vertebrates (e.g., amphibia, reptiles) and in very young mammals, growth in length is largely independent of the hypophysis. This is also true of tissue cultures in vitro where mammalian cells can proliferate in the absence of somatotrophin.

Very young rats, for instance, continue to grow, irrespective of their size at the time of the operation, until they reach a weight of approximately 75 gm.



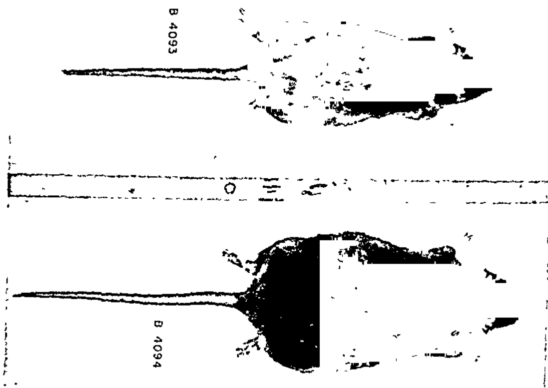
Growth curves of hypophysectomized female rats
(Courtesy of Dr. C.-H. Li)

The experimental animal received 0.10 mg of somatotrophin/day during first 140 days, the daily dose was then increased to 0.20 mg.



Growth curves of normal "plateau" female rats
(Courtesy of Dr. C.-H. Li)

The experimental animal received 0.40 mg of somatotrophin/day during the first 23 days, this dose being gradually raised to 2.0 mg./day.



Effect of somatotrophin on intact rat. Typical photograph of a normal 'plateau' rat, that is one having reached a weight at which normal growth is almost arrested (top) and similar animal after 432 days of treatment with somatotrophin (Courtesy of Dr C.-H. Li)

On the other hand, in rats hypophysectomized after they have reached the weight of 75 gm., growth ceases immediately upon ablation of the hypophysis. It is not known why the lowest stages, both in the ontogenetic and phylogenetic scale of development, are independent of pituitary growth-hormone.

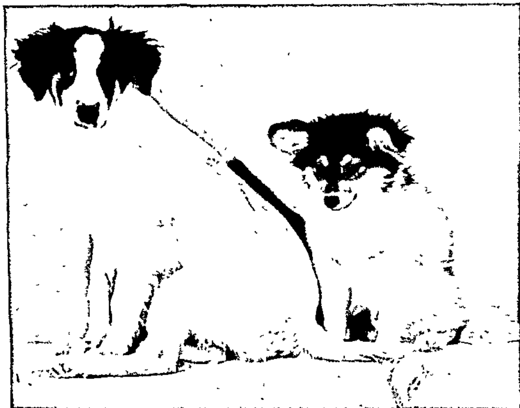
It has been ascertained that the growth-promoting effect of the pituitary is due to a hormone of the anterior-lobe, since growth in length is re-initiated in hypophysectomized animals by anterior, but not by posterior or middle-lobe extracts. As outlined in the section on the chemistry of the anterior-lobe hormones, somatotrophin is a chemically distinct hormonal principle which has been prepared in pure form (See pp. 210, 215, 216.)

In intact animals, somatotrophin causes fairly proportionate growth of all tissues and thus produces gigantism. Its effect upon the longitudinal growth of bones is principally due to a specific action upon the junction cartilage plates in which it promotes cell proliferation and subsequent ossification. However, it also stimulates subperiosteal growth in width and proliferation of soft tissues. It exerts no specific effect upon cells controlled by special trophic hormones (e.g., thyroid, adrenal cortex, gonads).

Corticotrophin inhibits growth-stimulation by somatrophin.

Blood-count. — HYPOPHYSECTOMY does not significantly influence the blood-count, although it tends to cause some degree of anemia and a fall in blood-volume.

Administration of CRUDE ANTERIOR-LOBE EXTRACTS, on the other hand, tends to raise the red-cell-count, as well as the blood volume. This action may be involved in the polycythemia and plethora of certain hyperpituitary syndromes such as Cushing's disease.



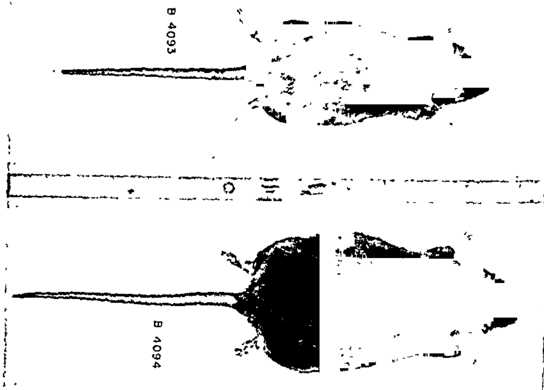
Effect of hypophysectomy in the dog. Two littermate female dogs, the one on the right was hypophysectomized two months before this picture was taken Their initial body weight was equal (3 Kg) while now the control dog weighs 7 Kg and the hypophysectomized animal (right) 3.0 Kg Note also typical fuzzy "puppy fur" of hypophysectomized animal

CORTICOTROPHIN normally causes a decrease in the lymphocyte-count, but in adrenalectomized animals and addisonian patients this effect cannot be elicited. Apparently, the effect of corticotrophin is mediated by the adrenal cortex whose corticoids are responsible for the lymphocyte-destroying effect

An increase in the red-cell-count and a change in the differential white-cell-count have also been observed in animals following isolated hypothalamic lesions.

Cardiovascular System.— In HYPOPHYSECTOMIZED animals, the heart and blood vessels are atrophic and the pulse rate and blood pressure are low Conversely, treatment of hypophysectomized or intact animals with crude ANTERIOR-LOBE EXTRACTS causes marked hypertrophy of the heart and blood vessels with an increase in blood pressure and pulse rate. These effects are partly mediated through the thyroid and can be duplicated by the administration of pure thyrotrophin or of thyroid-hormone itself. However, even in thyroidectomized animals some increase in heart weight can be obtained by anterior-lobe preparations, so that the effect cannot be regarded as solely mediated by the thyroid It is not yet known, which of the other hypophyseal principles participates in this effect.

Upon continued treatment with large doses of crude anterior-lobe extracts, severe hypertension, periarteritis nodosa, myocardial (Aschoff[7]) nodules and even coronary infarcts have been produced All these changes are especially readily obtained in rats, sensitized to these toxic effects by unilateral nephrec-



Effect of somatotrophin on intact rat. Typical photograph of a normal "plateau" rat, that is one having reached a weight at which normal growth is almost arrested (top) and similar animal after 432 days of treatment with somatotrophin (Courtesy of Dr C.-H. Li.)

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the sense organs. On the other hand, lesions to the hypothalamic nuclei may cause hypersomnia, and narcolepsy (sometimes with catapleхy). It is very doubtful whether there is a "sleep center" in the hypothalamus, but it is well established that this entire region plays an important part in the mechanism of sleep.

It has been claimed that INTERMEDIN is responsible for the migration of melanin granules in the retina, which is essential for dark-adaptation of the eye. This is very controversial, however, since it is known that hypophysectomy does not interfere with dark-adaptation.

POSTERIOR-LOBE EXTRACTS may cause profound, generalized depression, if administered in very large doses It is of diagnostic importance that vasopressin — especially when given after abundant water ingestion — causes convulsions in epileptics, but not in normal individuals Vasopressin (but not oxytocin) injected directly into the cerebral ventricles of monkeys and man causes pronounced, generalized vasodilatation, allegedly due to direct stimulation of the adjacent autonomic centers

Digestive System. — HYPOPHYSECTOMY causes profound atrophy of the entire gastrointestinal system, including the liver and the exocrine pancreas. Furthermore, hypophysectomized animals have a great tendency to develop the acute gastric ulcers characteristic of the alarm reaction Ulceration of the esophagus, stomach and duodenum, as well as disturbances in intestinal motility are also frequently observed following hypothalamic lesions.

Crude ANTERIOR-LOBE EXTRACTS cause an increase in the thickness and length of the gastrointestinal tract; this is accompanied by a marked hypertrophy and hyperplasia of the liver and the acinous tissue of the pancreas (The effect of pituitary extract upon the Langerhans islets has been discussed in the section on the pancreas) Certain impure anterior-pituitary extracts cause fat deposition in the liver, an effect which has sometimes been ascribed to a special "ketogenic or fat-metabolism hormone." Since adrenalectomy prevents this fat deposition, the latter is more probably due to corticotrophin. After partial hepatectomy, the compensatory hypertrophy of the hepatic remnant is greatly inhibited by hypophysectomy and accelerated by anterior-lobe extracts.

POSTERIOR-LOBE EXTRACTS have no specific effect upon the morphologic development of the digestive system. The influence of posterior-pituitary extracts on the motility of the intestine is variable. It depends upon the animal species, the type of anesthetic used and other experimental conditions. In human subjects with enterostomies (artificially placed fistulæ between intestine and skin), it has been found that pituitary-extract (probably because of its vasopressin content) markedly stimulates peristalsis, both in the colon and in the ileum. This increase in motility is unaccompanied by any effect upon the constant tonus. If moderate doses (not exceeding 20 units) of posterior-pituitary extract are used, the action rarely lasts longer than 90 minutes Nevertheless, vasopressin is often useful in the relief of intestinal paresis and distension after abdominal operations and febrile infections; at certain dose-levels it can also cause contraction of the biliary passages.

Skin and Appendages. — In fish, amphibia and reptiles HYPOPHYSECTOMY causes blanching of the skin, due to persistent contraction of the cutaneous melanophores This may be accompanied by a decrease in the number of melanin granules and an expansion of the light xantholeukophores. Consequently, the animals become unable to adapt their coloration to their background. The change is apparently due to intermediate-lobe deficiency, since isolated removal of the intermediate-lobe alone has a similar effect, while selective anterior

tomy and high-sodium, high-protein diets (see : General-Adaptation-Syndrome). These latter effects appear to be mediated by the adrenal cortex, since they cannot be elicited in adrenalectomized animals. However, as they have not yet been produced with pure corticotrophin, it is possible that other principles in the crude anterior-lobe extracts are also essential.

VASOPRESSIN causes constriction of the coronary arteries with rather characteristic changes in the E.C.G. and in the cardiac output. The latter is greatly increased following an initial transitory decrease.

Only under certain conditions, especially in anesthetized animals (e.g. in the ether-anesthetized cat or dog), does vasopressin cause a marked rise in blood-pressure; in non-anesthetized animals and man, the pressor effect is minimal or replaced by an actual drop in blood pressure with bradycardia. Not even all anesthetics permit the production of increased blood pressure by posterior-pituitary extract The pressor effect is not mediated by the nervous system, since it can occur after destruction of the brain or spinal cord and after paralysis of the vasomotor ganglia by nicotine Probably the pressor effect depends largely upon an increase in the capillary tonus, and to a lesser degree upon constriction of larger arteries and arterioles. To some extent it may even act by increasing the production of renal pressor substances since it causes marked constriction of the renal arteries, and this is known to stimulate the pressor-hormone production of the kidney.

Vasopressin has been recommended to combat hypotension in various types of shock, but because of the variability of the pressor response and the danger of further diminishing the already low blood pressure, it should not be administered in such cases.

It is questionable whether vasopressin plays any important part in the maintenance of the normal blood pressure, since removal of the posterior-lobe does not cause hypotension.

Lymphatic System. — In HYPOPHYSECTOMIZED animals, the thymus and other lymphatic organs are usually of moderate size. They are not completely atrophic nor do they show the excessive development observed after adrenalectomy. However, after hypophysectomy, as after adrenalectomy, exposure to various types of stress fails to elicit the usual alarm reaction type of acute thymus and lymphatic organ involution This is apparently due to a lack of defensive corticotrophic hormone secretion.

Hypophysectomy inhibits while hypophyseal extracts stimulate erythrocyte production in the bone marrow. The size of the spleen is markedly diminished after hypophysectomy and increased by crude anterior-lobe extracts.

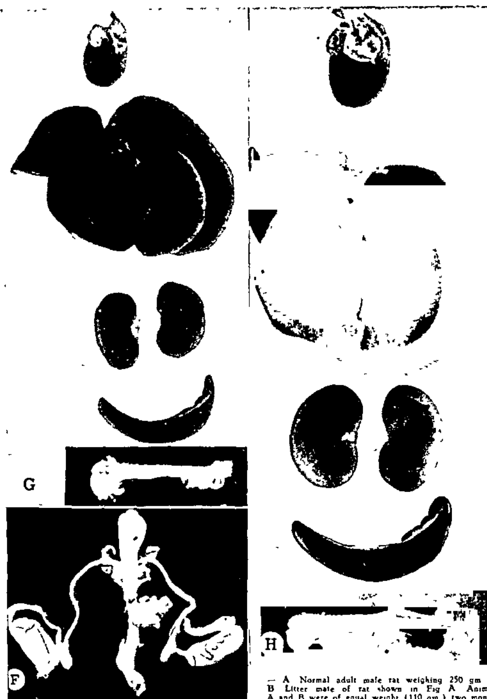
CORTICOTROPHIN injections cause speedy involution of the thymus — and to a lesser extent of other lymphatic organs — both in hypophysectomized and in intact animals

SOMATOTROPHIN is definitely "thymotrophic" and certain impure anterior-lobe extracts even prevent thymus atrophy during the alarm reaction.

THYROTROPHIN also stimulates the growth of lymphatic organs (as does thyroid hormone), hence the effect of impure anterior-lobe extracts is variable, depending upon the relative proportions of corticotrophin, somatotrophin and thyrotrophin which they contain.

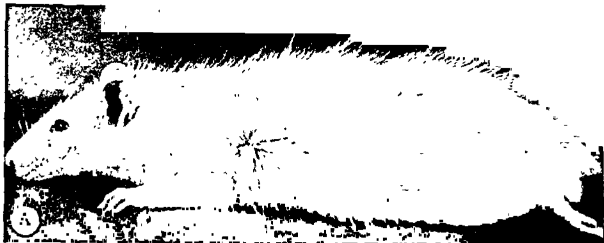
Muscles. — Anterior-lobe removal and complete hypophysectomy decrease, while anterior-lobe implants increase the contracture of the rectus abdominis muscle (frog) normally elicited by acetylcholine. Myograms of somatotrophin-treated rats revealed no improvement in muscular strength in spite of greater size.

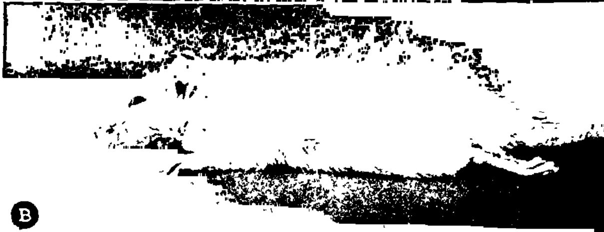
Nervous System and Sense Organs. — HYPOPHYSECTOMY causes no clear-cut changes in the nervous system or



— A Normal adult male rat weighing 250 gm — B Litter mate of rat shown in Fig A Animals A and B were of equal weight (110 gm) two months earlier
retard

rat weighed 86 gm — C Base of the skull (with pituitary) thy
shown in Fig A — D Base of the skull (note absence of p





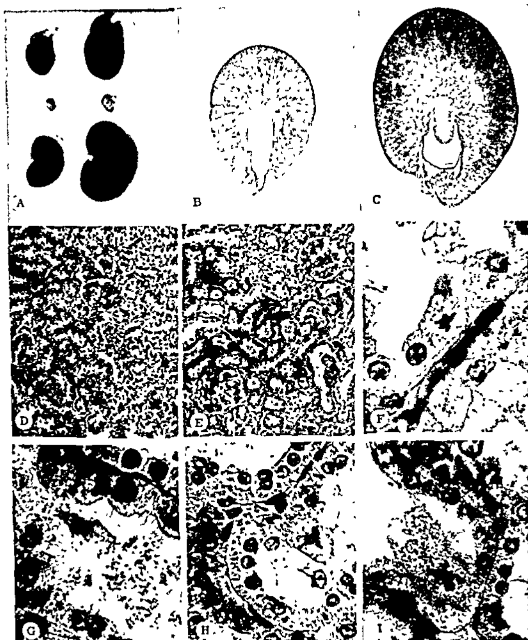








Effect of hypophysectomy on the organs of the rat. (Cont d)



Renotrophic effect of combined treatment with anterior-pituitary extract and thyroxin. — A. Macroscopic aspect of heart, adrenal and kidney of a control (left) and an experimental animal, the latter was treated with lyophilized hypophyseal tissue and thyroxin for 20 days — B and C. Low magnification of cross-sections through the kidney of a control (B) and

received the hypophyseal preparation plus thyroxin Note various types of mitotic divisions, budlike protrusion of cytoplasm reminiscent of apocrine secretion (F), a cell in mitotic division in the process of being discharged into the lumen (G), several binucleated cells and marked anisocytosis indicative of rapid proliferation (After Selye et al Canad Med Assoc J 52 571 1945)

or posterior-lobe removal does not produce blanching of the skin.

In certain snakes, *hypophysectomy* causes almost continuous moulting of the skin at irregular intervals. This is apparently due to lack of thyrotrophin, since thyroidectomy exerts a similar effect.

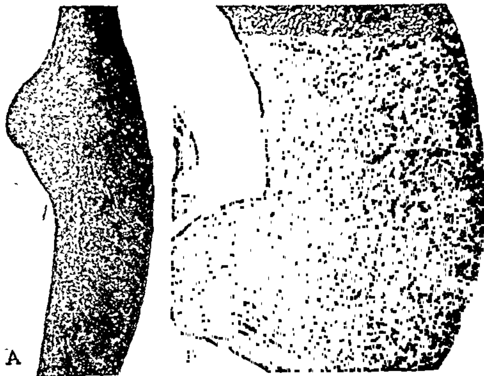
In mammals, the cutaneous changes after hypophysectomy are less obvious; there is some degree of skin *atrophy, often accompanied by loss of hair.* Hypophysectomy in immature animals causes permanent retention of the very fine "puppy fur." (See . p. 241.)

In birds with sex-specific plumage types (e.g., fowl) hypophysectomy causes plumage changes reminiscent of those produced by gonadectomy. However, hypophysectomy also eliminates the plumage-influencing effect of the thyroid and hence the resulting changes are complicated by those of thyroid-deficiency.

Treatment with crude ANTERIOR-PITUITARY EXTRACTS results in excessive *development of the sebaceous glands.* The intense acne often seen in hyperpituitary syndromes (e.g., Cushing's disease) is probably related to this effect.

Administration of INTERMEDIN causes expansion of the melanophores in poikilothermic animals and thus leads to darkening of the skin. VASOPRESSIN elicits profound pallor, even in *mammals, presumably due to constriction of* the cutaneous capillaries.

Urinary System. — HYPOPHYSECTOMY causes pronounced atrophy of the kidney in all animal species. It also interferes with the compensatory hypertrophy of the remaining kidney, in the event of unilateral nephrectomy. It has not yet been established whether there is a special "renotrophic anterior-lobe hormone," but it is certain that the action upon the kidney is due to the anterior-lobe.



Renotrophic effect of anterior-pituitary extract. — *A. Low magnification of a cross-section* through a rat kidney 20 days after ureter ligature Note marked pressure atrophy of kidney tissue, which is reduced to a very thin layer — B Cross-section through a similar rat kidney 20 days after ureter ligature In this animal renal atrophy was inhibited by daily treatment with renotrophic anterior-pituitary extract (After H Selye and C Hollett J Urol 53 495 1945.)



Renal infarct produced by vasopressin. Several belt-like anemic infarcts in the kidneys of a female adult rat which received 50 U S P units of "surgical pituitrin" twice daily on two successive days The distribution of the infarcts corresponds to the territories of the larger renal arterial branches

terior-pituitary preparations do not necessarily run parallel, but it has not yet been possible to completely separate the two principles.

Large doses of vasopressor posterior-lobe extracts cause multiple anemic infarcts in the kidney, presumably due to their vasoconstrictor effect. For reasons which are not yet understood, pretreatment with folliculoids greatly increases the incidence and severity of renal infarction following vasopressin administration

Accessory Sex-Organs. — Almost all the actions of anterior-lobe extracts upon the accessory sex-organs are mediated by the gonads These indirect actions have been discussed in detail in the chapters on the ovary and testis, hence they need not be reviewed here. However, a few accessory sex-organs are responsive to direct stimulation with pituitary hormones

Thus, for instance, the MAMMARY GLANDS can be directly influenced by *anterior-lobe hormones.* Impure anterior-lobe extracts stimulate mammary growth even in gonadectomized (male or female) animals, due to a so-called "mammogenic action" This effect is greatly enhanced by simultaneous administration of various steroid hormones (folliculoids, luteoids, testoids), but it is manifestly not exclusively mediated through the gonad.

The effect of luteotrophin (prolactin) upon milk secretion is likewise independent of the gonads since it is not abolished by ovariectomy; indeed, even normal lactation is maintained (often actually increased) after spaying.

The galactagogic action of *posterior-pituitary extracts* is also direct; it depends merely upon the stimulation of the smooth muscle cells in the mammary gland and the resultant expression of accumulated milk. Unlike luteotrophin,



Effect of combined treatment with pituitary extract and Δ^5-Pregnenolone upon the preputial glands of the rat. — A. Preputial glands of a control, not treated female [this as well as all other animals of this series (A-D) were hypophysectomized and ovariectomized in order to avoid complication of the results by endogenous ovarian or pituitary hormones] — B. Slight enlargement of the preputial glands by Δ^5-pregnenolone treatment — C. Marked enlargement of preputial glands due
pituitary extract —
this illustrates peripl

Treatment with crude ANTERIOR-LOBE EXTRACTS restores the atrophic kidney of the hypophysectomized animal to normal and may even induce marked hypertrophy and hyperplasia of the kidney in intact animals. This action is not entirely due to thyrotrophin, since it is only diminished and not prevented by thyroidectomy. Nevertheless, the thyroid plays an important rôle in this "*renotrophic effect*," since simultaneous treatment with anterior-pituitary extract and thyroid hormone elicits a much more pronounced renal enlargement than can be obtained by either of these preparations alone. The renotrophic steroids (e.g., testosterone) likewise potentiate the kidney-stimulating effect of crude anterior-lobe extracts. In animals treated with renotrophic anterior-pituitary preparations, there is marked hyperplasia and hypertrophy of the epithelium in the proximal and distal convoluted tubules, as well as enlargement of the renal glomeruli. This effect is not to be confused with the nephrosclerotic action, which is presumably due to corticotrophin and will be discussed below. Unlike the latter, the renotrophic action is not markedly influenced by the sodium content of the diet.

Renotrophic anterior-lobe extracts also increase the functional capacity of the kidney as judged by clearance tests and render the organ more resistant to the pressure atrophy normally produced by occlusion of the ureter. (See p. 246.)

Impure anterior-pituitary extracts, however, may have an opposite, kidney-damaging effect characterized by *nephrosclerosis*. This action is particularly evident in animals sensitized by *unilateral nephrectomy and given diets* rich in sodium and protein. It is accompanied by hypertension and is apparently due to the same principle which elicits periarteritis nodosa and cardiac (Aschoff ?) nodules. The nephrosclerotic effect cannot be elicited after adrenalectomy and is apparently due to the corticotrophin content of the crude preparations. Simultaneous administration of thyroid hormone aggravates the nephrosclerotic action of pituitary extracts, and hence the thyrotrophin content of the crude preparations *probably* also plays a rôle (see : General-Adaptation-Syndrome). The renotrophic and nephrosclerotic actions of crude an-



Production of nephrosclerosis by anterior-pituitary extract. — **A.** Section through the kidney *of a rat sensitized* by sodium and unilateral nephrectomy and treated with lyophilized anterior-pituitary material during a period of four weeks. Note large, partly hyalinized, glomerulus ... of the field, there are ... e kidney of a similarly ... mpletely prevented by ... Na-depletion

(After C. E. Hall and H. Selye. Rev. Can. de Biol. 4: 197, 1945.)

Treatment with crude ANTERIOR-LOBE EXTRACTS or gonadotrophins, especially luteotrophin, tends to prolonq the normal duration of gestation, presumably because of an increased and protracted progesterone secretion.

Lactation. — After delivery, milk secretion commences in a fully-developed mammary gland, even in the absence of the anterior-lobe, but these secretory phenomena soon cease and the breasts involute. Probably during the second half of gestation the placenta is sufficiently well-developed to take over most of the endocrine functions of the anterior-hypophysis. Through the production of luteotrophin the placenta maintains the structure and function of the large corpora lutea of pregnancy; these, and the placenta, produce adequate amounts of progesterone to maintain the developing ovum. After termination of the normal "life span" of the placenta, the latter becomes detached and transitory milk secretion ensues as a "withdrawal phenomenon." The maintenance of the mammary glands in the hypophysectomized, pregnant animal has been ascribed to placental "mammogenic hormones," and milk secretion at parturition to placental "prolactin."

Hypophysectomy during lactation causes immediate cessation of milk secretion, unless adequate prolactin therapy is immediately initiated; indeed even active prolactin preparations rarely suffice to maintain adequate lactation after hypophysectomy for more than a very brief period.

Metamorphosis. — In hypophysectomized tadpoles metamorphosis does not occur, unless either thyrotrophin or thyroid hormone is administered Thyrotrophin (through its action on the thyroid) can even accelerate normal metamorphosis in intact amphibia.

HYPOPHYSEAL HORMONE CONTENT OF BODY FLUIDS AND TISSUES

Blood and Urine. — A good deal of work has been done concerning the GONADOTROPHIN content of blood and urine, because of their diagnostic value and the comparative ease with which such determinations can be performed.

In *newborn children*, the body fluids contain appreciable quantities of LH which is presumably of placental origin. A few days later, however, only traces of gonadotrophins can be demonstrated in the blood and urine until *puberty*, when the urinary gonadotrophin excretion increases in both sexes and becomes approximately the same as in adults.

In normal *adult women* the urine always contains at least traces of gonadotrophins, but appreciable quantities (2-25 I.U./L.) of both FSH and LH have only been demonstrated during the 10th-14th day of the cycle, that is at the time of ovulation. A second — less constant — peak in gonadotrophin excretion is claimed to occur just before or during menstruation. (See : p. 806.)

Normal *adult men* excrete only traces of gonadotrophin without any cyclic variations in the daily amount. Most investigators report between 5 and 25 M.U./L. of FSH, but only traces of LH, if any.

In women with *menstrual disorders* gonadotrophin elimination is often abnormal, for instance a midmenstrual peak is generally absent in patients with anovulatory cycles. In primary hypoövarianism both blood and urine contain greatly increased quantities of gonadotrophin Conversely, in secondary ovarian failure due to anterior-lobe deficiency, the gonadotrophin elimination is diminished.

Large quantities of gonadotrophin (mainly FSH) are also eliminated during the *menopause* and in women following surgical or X-ray *castration*. The absolute values obtained by various

posterior-pituitary extract does not alter the total amount of milk produced.

The stimulation of the PREPUTIAL GLANDS, especially in the rat, is likewise under the direct control of some pituitary hormone. As previously mentioned, anterior-lobe extracts cause an increase in the size of these glands in both sexes, irrespective of the presence or absence of the gonads. Certain steroids (e.g., Δ^5-pregnenolone), which could come from the gonads, cause only mild preputial gland stimulation in themselves but they greatly enhance the corresponding effect of anterior-lobe extracts. As in the case of the mammary gland, there appears to be a peripheral synergism between the steroid and the anterior-lobe hormone It has not yet been determined which, among the anterior-lobe principles, is responsible for this effect

The contractions of the UTERUS are greatly stimulated by oxytocin. Small doses merely augment the tonus and increase the amplitude, while larger doses cause tetanic contractions, which may last several minutes. In certain animal species, especially the rabbit, folliculoids increase, while luteoids diminish the contractility of the uterine musculature and its response to oxytocin. It is noteworthy, however, that the human uterus responds to oxytocin at least as well during the luteal, as during the follicular phase of the cycle and its contractions are not inhibited by simultaneous progesterone administration Even during pregnancy the human uterus contracts under the influence of oxytocin.

It has been claimed that increased secretion of oxytocin is responsible for the intense uterine contractions during normal delivery. In hypophysectomized animals, the process of delivery is often delayed and the contractions tend to be weak; yet parturition can occur after complete ablation of the hypophysis, so that the posterior-lobe is not indispensable for this process.

Clinically, oxytocin should only be used : (1) for the induction of labor at term if this fails to occur spontaneously: (2) to control hemorrhage after delivery in the case of uterine atony, (3) to hasten the normal involution of the uterus during the puerperium The administration of oxytocin is strictly contra-indicated during the first and second stages of labor, because the type of contractions elicited is too intense and sustained. If the hormone is given before suitable dilatation of the cervix and rupture of the membranes, it may cause severe laceration of the cervix, rupture of the uterus or excessive trauma to the infant. In the event of prolonged tetanic contraction of the uterus, the fetus may even die from asphyxia

The addition of thymus extract to posterior-lobe extracts was recommended by some physicians, but the efficacy of this practice has not been proven.

As has been stated above, the PLUMAGE of certain birds exhibits a sexual dimorphism This is apparently under the control of the hypophysis and due to the influence of certain anterior-lobe hormones, mainly the gonadotrophins and thyrotrophin.

Sexual Cycle. — Hypophysectomy abolishes, while administration of impure anterior-lobe extracts, or of purified gonadotrophins, deranges the sexual cycle both in animals and in man; this is due to the resulting ovarian changes (see : p 374) Intermediate and posterior-lobe extracts exert no specific effect upon sexual cyclicity.

Pregnancy. — Hypophysectomy during the first half of gestation causes abortion in most animal species, during the second half of pregnancy, however, the pituitary may be removed in some animals (e g , rat) without interfering with the subsequent progress of gestation, the growth of the embryo and the development of the mammary glands Delivery is usually delayed (interference with oxytocin production ? delayed involution of the pregnancy corpora lutea ?) and sometimes the embryo dies in utero In other instances, however, delivery of normal young has been observed

It is noteworthy that the dysgerminoma or "false seminoma" of the ovary or testis likewise tends to augment LH excretion; this, as well as certain histologic characteristics of these tumors (see : p. 449) intimate a close relationship to neoplastic placental cells. That women with *uterine carcinomas* frequently also excrete excessive amounts of FSH is most probably due not to the tumor itself, but to the fact that the majority of these patients are of menopausal age.

In cases of so-called *pseudopregnancy* with corpus luteum cysts, the urinary gonadotrophin excretion is likewise high, thus increasing the difficulty of differentiating between this condition and pregnancy.

Increased urinary gonadotrophin excretion also occurs in the *male climacteric, cryptorchidism, the "hypergonadotrophic eunuchoidism without a-Leydigism"* (Klinefelter syndrome) and less regularly in patients with *anterior-pituitary tumors, increased intra-cranial pressure*, anatomic *lesions in the hypothalamus, adrenal-cortical tumors* and *hyperthyroidism*

Injection of PMS into monkeys or rats does not cause any elimination of gonadotrophin in the urine, although these species excrete injected *LH* prepared from human urine or blood In the pregnant mare, the urine is likewise almost free of gonadotrophins in spite of the high blood concentration, hence it appears that the FSH of pregnant mare serum cannot pass through the renal barrier. Unlike LH, PMS is as effective in single as in divided doses This may likewise be due to the non-excretability of the latter and partly also to the accompanying proteins, which delay its absorption from the site of injection. Experiments in the rabbit and gelding show that injected *PMS* is demonstrable in the blood for several days without being excreted in the urine Its final disappearance from the blood is apparently due to destruction by the cells of the organism, but it has not yet been possible to determine the exact site at which this destruction occurs The gonads (the specific target organs of this hormone) are not involved in this destruction, since disappearance from the blood proceeds as rapidly in gonadectomized as in intact animals This is in accordance with the previously expressed view (see· General Endocrinology) that hormones are not 'utilized' by their target organs while they exert their physiologic effects (p 20, 21).

Much less is known about the concentration of other hypophyseal hormones in the blood and urine, mainly because the pertinent test methods are more complicated and less accurate. It has been shown however, that CORTICOTROPHIN excretion is high in Cushing's disease, while THYROTROPHIN elimination rises in some patients with thyrotoxicosis in accordance with expectations. Normally, only negligible traces of corticotrophin, thyrotrophin, or any other anterior-lobe hormones are demonstrable in the urine of man.

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Intracarotid injection of hypertonic (25%) NaCl in dogs causes excretion of an anti-diuretic substance in the urine. Simultaneously, there is oliguria due to increased tubular reabsorption Filtration remains normal, as judged by creatinine clearance. Probably *NaCl stimulates the hypothalamus-pituicyte* system directly.

Hypophysis. — Comparatively few systematic studies have been made with the object of determining the NORMAL, absolute concentration of the various *anterior-pituitary hormones* in the pituitaries of different species. It has been shown, however, that the corticotrophin content of the pituitary diminishes in the following order : pig, man, sheep, horse, cattle; while the prolactin content decreases in the order · sheep, ox, man, pig, horse It is also known that cattle pituitaries are comparatively rich in growth hormone, but poor in gonado-

investigators are not readily comparable, because of differences in the bioassay *technics and the definitions of the units.* It has been stated however, that in menopausal or castrate women, the urine contains anywhere between 100 and 500 M.U./24 hrs. or 25-75 I.U./24 hrs, which is several hundred per cent above the maximum of the normal urinary excretion. All these observations are in accordance with the assumption that in the absence of gonadal hormones, the pituitary produces an excess of gonadotrophins in a, usually futile, effort to compensate for the ovarian deficiency by stimulating the *growth of gonadal tissue.*

In *pregnant* women extraordinarily large quantities of gonadotrophins appear in the blood and urine almost immediately after the first missed period. Between the 5th-6th week an average of 16,000 M.U./L. are found in the blood, but some investigators reported values as high as 500,000 I.U./L. of blood on the 14th day of pregnancy. The peak of urinary excretion of gonadotrophins (during pregnancy almost exclusively LH) is also reached between the 20th and the 60th day after the first missed period. At the time of maximum excretion, the urine contains about 60,000 I.U./L. After the 67th day the hormone level falls sharply and reaches a level of about 5,000 I.U./L. on the 140th day. The urinary concentration of LH tends to be considerably higher in multiple pregnancies, apparently because of the presence of two or more placentæ. (See . p. 821)

Pregnant animals of most species do not excrete any appreciable amounts of gonadotrophins during gestation. In the mare the blood gonadotrophin content (mainly FSH) rises rapidly between the 37th and 42nd day of gestation and reaches a peak of about 50,000 I.U./L between the 42nd and 80th day; it almost disappears completely from the blood between the 130th and 180th day. The high concentration of FSH in pregnant-mare-serum makes the latter a valuable source for the preparation of this hormone (usually referred to as "PMS gonadotrophin"). Curiously, almost none of this blood gonadotrophin is eliminated in the urine of the pregnant mare.

It is noteworthy that in *ectopic pregnancy* the Aschheim-Zondek test, or its modifications, often give negative results. This is probably due to the fact that systematic hormone studies are rarely performed on patients with ectopic pregnancies until the appearance of symptoms; by that time the placenta is usually detached so that the gonadotrophins are no longer transmitted to the mother. As long as the placenta is viable, there is no reason to believe that it would produce less gonadotrophin if it were ectopically located.

In the event of *fetal death,* the LH content of blood and urine frequently declines to very low levels. Since LH is produced by the chorion and not by the fetus, it is debatable whether death of the latter is the cause or the result of diminished LH production. It is possible that damage to the placenta caused by fetal death diminishes LH production by the chorionic cells, but conversely, a deficient LH production may adversely affect the fetus.

In *hyperemesis gravidarum,* as well as in pre-eclampsia and eclampsia, the LH content of the blood is often extremely high, while that of the urine may be normal, high or low.

Tumors of placental tissue (chorionepitheliomas, hydatidiform moles) and *teratoids* (e.g., in the ovary or testis), which may also contain chorionic elements, likewise tend to raise blood and urine gonadotrophin titers. This is of considerable diagnostic value in patients in whom pregnancy can be excluded. Even in pregnant women, the LH elimination is usually much higher if there is placental neoplasia, but here the difference is less striking and hence not always sufficient to formulate a diagnosis.

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trophin; while *pig pituitaries are a rich* source of gonadotrophic activity.

The pituitary of the rat contains *unusually large quantities of thyrotrophin*, while that of the guinea-pig is poor in this principle; conversely, the rat thyroid is very insensitive while that of the guinea-pig is especially responsive to stimulation by thyrotrophin.

It is noteworthy, that although the human pituitary has no distinct intermediate-lobe, it contains very large amounts of *intermedin* within the anterior-lobe.

Oxytocin and *vasopressin* are especially plentiful in the posterior-lobe, but traces have also been demonstrated in the stalk and tuber cinereum.

Perhaps too much emphasis has been placed upon changes in the hormone concentration of the pituitary as reliable indicators of hormone production. The concentration of a hormone in the pituitary can rise due to increased production or decreased discharge into the blood. Hence a change in the hormone content of the gland gives no evidence of the amount produced. Nevertheless, it is interesting to note that GONADECTOMY in either sex increases the gonadotrophin content of the hypophysis, simultaneously with the proliferation of the "castration cells" and increased urinary gonadotrophin elimination. Hence, in this case there is adequate evidence of a rise in gonadotrophin production as a result of gonadectomy. This view is further supported by the fact that folliculoids and testoids diminish the high gonadotrophin content of the pituitary and urine in castrates of either sex

Similarly, THYROIDECTOMY increases, while thyroid hormone administration decreases the thyrotrophin content of the anterior-lobe. It has been claimed that THIOUREA decreases the thyrotrophin content of the pituitary, but the evaluation of this observation must await additional data.

During the latter half of GESTATION, the prolactin content of the pituitary begins to rise quite considerably, but after delivery, with the onset of LACTATION, this increase suddenly becomes still more pronounced.

The stimulus of *nursing* influences the luteotrophin content of the pituitary, since in postpartum rabbits the initially high prolactin concentration of the hypophysis declines more rapidly if the young are removed than if they are permitted to nurse. Folliculoids tend to increase the prolactin content of the pituitary even when given in doses sufficient to inhibit milk secretion.

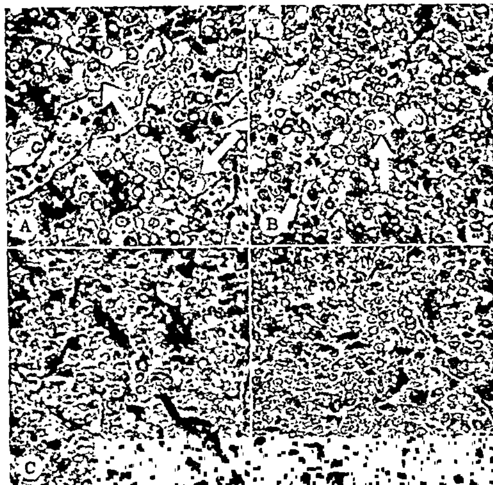
Placenta. — The placenta is a rich source of hypophysoid hormones. It contains and secretes LH, FSH, luteotrophin and perhaps even "mammogenic hormone." The human placenta elaborates especially large quantities of LH, while the mare's placenta produces predominantly FSH. The placental (chorionic) cells of most other animal species elaborate comparatively small quantities of FSH and LH, but there is adequate proof of a high luteotrophin production by the chorionic cells of the rat and rabbit placenta. Data concerning the production of other pituitary hormones by placental cells is less convincing.

Plants. — It is interesting that gonadotrophic extracts have also been prepared from various plants (alfalfa-leaf meal, oak leaves, corn). These produce ovulation in the rabbit following intravenous injection, and some of them exhibit a gonadotrophic action even in the hypophysectomized male rat

STIMULI INFLUENCING HYPOPHYSEAL STRUCTURE

Extirpation of Endocrine Glands. — ADRENALECTOMY causes no characteristic changes in the pituitary, although in the rat, some investigators report a decrease in eosinophils.

Following PARTIAL HYPOPHYSECTOMY, the remaining anterior-lobe tissue shows marked signs of compensatory hypertrophy This is particularly obvious in the dog and rabbit, in which the



Effect of castration ... cells with beginn... beside the nucleu... Section taken 16... vacuoles — C ... 50 γ/day of ... rat similar to ... autop...

anatomically distinct pars tuberalis undergoes marked proliferation following ablation of the main pituitary body. In man, hypertrophy of the pars tuberalis has also been observed following destruction of the pituitary by disease. Regenerative phenomena in the intermediate and posterior-lobes are much less obvious.

Castration, both in the male and female, produces essentially similar pituitary changes in animals of the same species. It is important to keep in mind, however, that the removal of the gonads causes qualitatively different changes in various species. Thus, in the rat, gonadectomy (in either sex) produces a marked hypertrophy and hyperplasia of the basophils, which is quite obvious as soon as 14 days after the operation. At this time, enlarged basophils are especially numerous in the immediate vicinity of the middle-lobe. After three to four months, they are found throughout the anterior-lobe. These cells develop from normal basophils which first enlarge, then their Golgi apparatus becomes particularly prominent, so that the negative Golgi image is clearly visible in the shape of a light ring. Later,

a large vacuole is formed in the cytoplasm of the cell in the Golgi region, the subsequent enlargement of this vacuole pushes the nucleus to one side, giving the cell the characteristic "signet ring" appearance: the cytoplasmic border represents the ring itself and a large nucleus on one side is reminiscent of the signet.

Since among all laboratory animals, castration changes are most obvious *in the rat, this species has been predominantly used for pertinent studies.* Perhaps too far-reaching conclusions have hence been drawn, regarding the abovementioned change in basophils and the increased gonadotrophic hormone production induced by castration. It is worth keeping in mind that in the majority of other animals (e g., birds, cat, dog, pig, rabbit), as well as in man, gonadectomy causes proliferation of the eosinophils, sometimes accompanied by an actual decrease in basophils; yet in other animals (e g., mouse) castration produces no conspicuous histologic change in the anterior-lobe. The only uniform effect of gonadectomy upon the pituitary of either sex, throughout the various animal species, is a more or less *selective enlargement of the anterior-lobe*, without significant influence upon either the intermediate or the posterior-lobe.

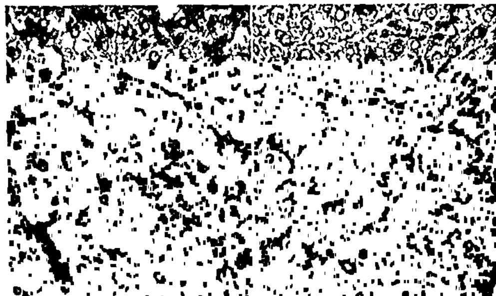
Administration of various *steroid hormones* to gonadectomized male or female rats inhibits the development of castration cells The folliculoids, testoids, luteoids, corticoids and spermatogenic steroids are decreasingly less active in the order mentioned, but the degree of their activity is identical in the two sexes From this, it has been concluded that the anti-castration-cell effect is subordinate to the folliculoid activity with which it runs parallel throughout the pharmacologic groups enumerated above In this connection, it is worth reemphasizing that the gonadotrophins (LH and FSH) unlike the gonadal hormones (folliculoids and luteoids in the female; testoids in the male) are not sex-specific. Correspondingly, the changes in anterior-lobe structure, accompanying increased gonadotrophin production, are the same in gonadectomized male and female animals and the inhibition of the castration changes can be accomplished by gonadal hormones of either sex, both in the castrate male and in the spayed female. *Ovarian or testicular transplants* likewise prevent the development of castration cells in either sex.

It has been claimed that *transection of the pituitary stalk* inhibits the formation of castration cells following subsequent gonadectomy in the rat, but administration of folliculoids succeeds in curing preexistent castration changes, even in a pituitary whose stalk has been severed. It has been concluded that innervation of the anterior-lobe is essential for the formation of castration cells, but not for their cure by folliculoids.

Lactation inhibits the development of castration cells in spayed rats, perhaps due to the nervous stimulus of nursing.

PARATHYROIDECTOMY causes no conspicuous change in the pituitary of most species, although in the rat, some investigators claim to have found an increase in the number of eosinophils following this operation.

THYROIDECTOMY, whether or not accompanied by parathyroidectomy causes very pronounced and typical lesions in the anterior-lobe, especially in the rat Among these, the most conspicuous is the formation of "signet-ring cells." These are similar to those produced by castration, but numerous small vacuoles appear after thyroidectomy instead of the single large one characteristic of the castration cell Furthermore, in the thyroidectomized rat, the number of acidophils tends to decrease. Although the qualitative changes in the pituitary are different in the various animal species, it may be said that thyroidectomy rather uniformly results in a selective increase in the weight of the anterior-lobe, without noteworthy changes in the intermediate- or middle-lobes



Effect of thyroidectomy upon the hypophysis. — A. Hypophysis of adult male rat 14 days after thyroidectomy Note "multiple vacuolization" of the hypertrophic cells (arrows); this helps to distinguish them from the castration cells, in which only a single large vacuole develops in the Golgi region — B. Hypophysis of a rat, similar to that shown in Fig A, but receiving 350 γ/day of thyroxin Note absence of "thyroidectomy cells".

In man, postoperative hypothyroidism likewise causes an increase in the pituitary weight, which is usually accompanied by the appearance of vacuolized basophils.

Administration of the various *steroid hormones* which are effective in curing the castration changes in the anterior-lobe of the rat do not influence the thyroidectomy cells, while conversely, *thyroid hormone* (thyroxin or desiccated thyroid) readily restores to normal the hypophysis of the thyroidectomized rat, but fails to influence the changes induced by castration.

Removal of OTHER ENDOCRINE GLANDS causes no constant, characteristic lesions in the pituitary.

Hormones. — Reports concerning the influence of PITUITARY PREPARATIONS upon the anterior-lobe are somewhat conflicting, probably because, up to now, comparatively little work has been done with pure hormones. Chronic treatment with crude, cattle anterior-lobe extracts causes involution of the anterior-lobe in the rat; this is probably due to compensatory atrophy Such extracts are poor in gonadotrophic potency.

Treatment, especially of immature females, with LH from pregnancy urine or placenta, causes an hypertrophy of the anterior-lobe, which runs approximately parallel with the resulting ovarian enlargement and fails to occur after spaying Since folliculoids enlarge the anterior-lobe, it is probable that the gonadotrophins stimulate it, through the folliculoids produced by the animal's own ovary. This is all the more likely, since very chronic treatment with LH produces vacuolized anterior-lobe cells, similar to "castration cells," at a time when antihormone formation results in a secondary ovarian involution

It is probable that anterior-lobe hormones can influence the pituitary in two ways . directly, causing compensatory atrophy of the anterior-lobe cells and indirectly, through the ovary, stimulating the anterior-lobe through the excess *formation of folliculoids.*

FOLLICULOIDS cause a very pronounced enlargement of the anterior-lobe in various animal species, especial-

a large vacuole is formed in the cytoplasm of the cell in the Golgi region. the subsequent enlargement of this vacuole pushes the nucleus to one side, giving the cell the characteristic "signet ring" appearance; the cytoplasmic border represents the ring itself and a large nucleus on one side is reminiscent of the signet.

Since among all laboratory animals, castration changes are most obvious in the rat, this species has been predominantly used for pertinent studies. Perhaps too far-reaching conclusions have hence been drawn, regarding the above-mentioned change in basophils and the increased gonadotrophic hormone production induced by castration. It is worth keeping in mind that in the majority of other animals (e g , birds, cat, dog, pig, rabbit), as well as in man, gonadectomy causes proliferation of the eosinophils, sometimes accompanied by an actual decrease in basophils, yet in other animals (e.g., mouse) castration produces no conspicuous histologic change in the anterior-lobe The only uniform effect of gonadectomy upon the pituitary of either sex, throughout the various animal species, is a more or less selective enlargement of the anterior-lobe, without significant influence upon either the intermediate or the posterior-lobe

Administration of various *steroid hormones* to gonadectomized male or female rats inhibits the development of castration cells The folliculoids, testoids, luteoids, corticoids and spermatogenic steroids are decreasingly less active in the order mentioned, but the degree of their activity is identical in the two sexes From this, it has been concluded that the anti-castration-cell effect is subordinate to the folliculoid activity with which it runs parallel throughout the pharmacologic groups enumerated above. In this connection, it is worth reemphasizing that the gonadotrophins (LH and FSH) unlike the gonadal hormones (folliculoids and luteoids in the female; testoids in the male) are not sex-specific. Correspondingly, the changes in anterior-lobe structure, accompanying increased gonadotroph production, are the same in gonadectomized male and female animals and the inhibition of the castration changes ca be accomplished by gonadal hormones of either sex, both in the castrate male and in the spayed female. *Ovarian or testicular transplants* likewise preve the development of castration cells i either sex.

It has been claimed that *transectio of the pituitary stalk* inhibits the forma tion of castration cells following subse quent gonadectomy in the rat, but ad ministration of folliculoids succeeds i curing preëxistent castration change even in a pituitary whose stalk has bee severed. It has been concluded that in nervation of the anterior-lobe is essen tial for the formation of castration cell but not for their cure by folliculoids

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vasion" of the posterior-lobe. In the anterior-lobe, the number of basophils is allegedly likewise increased. However, this process is common in normal individuals and hence difficult to evaluate. It is perhaps more significant that basophilic adenomas in the anterior-lobe are often accompanied by hypertension and secondary contracted kidney. The frequent occurrence of hypertension with nephrosclerosis in Cushing's disease, in which basophilic adenomas are found in the pituitary, is likewise noteworthy in this connection. In view of recent experimental work, showing that anterior-pituitary extracts can produce hypertension and nephrosclerosis (see experimental data on p. 248), these observations are rather significant. While it is true that not all cases of renal hypertension are accompanied by obvious lesions in the anterior-lobe, the bulk of the published data suggests some relationship between basophilism and renal hypertension.

ADIPOSITY, especially that of the constitutional type, is frequently accompanied by basophilia of the anterior-lobe and small chromophobe or basophil adenomas are unusually common in such patients. Perhaps the adiposity of Cushing's disease is also related to basophil proliferation

In CHORIONEPITHELIOMAS, which produce excessive amounts of gonadotrophins, the pituitary shows "pregnancy changes"

Increased INTRACRANIAL PRESSURE, due to hydrocephalus, brain tumors, etc., is usually associated with hyperplasia of the anterior lobe. Only if the causative process destroys the stalk is there atrophy of both anterior and posterior lobes (*E. J. Kraus*).

It has been claimed that specific lesions occur in the anterior-lobe of patients suffering from DEMENTIA PRECOX, EPILEPSY, PROGRESSIVE PARALYSIS, ENCEPHALITIS EPIDEMICA and OTHER NERVOUS DISEASES, but these lesions are not very characteristic. In ECLAMPSIA, basophilic invasion of the posterior-lobe, accompanied by proliferation of the basophils in the anterior-lobe, has also repeatedly been reported, although it is not very constant or conspicuous.

In patients bearing MALIGNANT TUMORS, degenerative changes have been seen in the anterior-lobe and in rats with transplantable carcinomas, large vacuolated cells are noted in the pars distalis. However, similar changes have also been produced by the injection of various protein extracts, and probably the decomposition of tissue in the necrotic tumor centers (rather than any specific humoral substance) is responsible for the pituitary lesions observed.

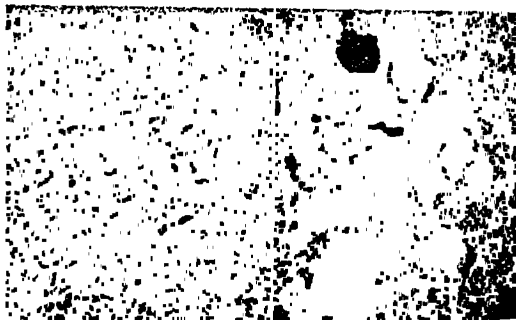
The hypophyseal lesions associated with various clinical forms of HYPO and HYPERPITUITARISM are discussed in the sections devoted to the latter; OTHER DISEASES rarely cause striking and specific changes in the hypophysis.

Diet. — Changes in diet may also lead to histologic lesions in the anterior-lobe, but it is often difficult to determine whether these are the direct result of the diet, or secondary consequences of the accompanying gonadal atrophy, adreno-cortical hypertrophy, etc.

AVITAMINOSIS-E induces castration changes in the pituitaries of male, but not of female rats, presumably because only in males do such diets cause gonad involution.

Nervous Stimuli. — In spite of the fact that the pituitary stalk carries numerous fibers to the pituitary, carefully performed stalk transections elicit no histologic change in the anterior-hypophysis. The positive findings of early investigators were probably due to incidental interference with the hypophyseal blood supply.

In animals in which copulation elicits pseudopregnancy (e.g., rabbit) the stimulus of mating decreases the eosinophil and basophil count. The chromophobes, on the other hand, become particularly abundant 5-6 days after mat-



Effect of folliculoids *upon hypophysis.* — A. Hypophysis of normal adult male rat (9 mg) — B. Hypophysis of adult male rat treated with 100 γ/day of α-estradiol during 9 months Note *cystic* cavernoma-like formation in the midst of chromophobe adenomatous anterior-lobe cells (54 mg).

ly in the rat and mouse. This is accompanied by degranulation of both the acidophils and the basophils, as well as by development of cell types similar to those seen in pregnancy (see p. 260).

In the event of chronic folliculoid treatment, chromophobe adenomas, with large cavernous blood sinuses develop in the anterior-lobe of the mouse and rat. These tumors may become so large that eventually the animals lose their sight due to pressure upon the optic chiasm and excessive intracranial pressure is the final cause of death. Malignant changes have never been observed in such neoplasms.

TESTOIDS have no pronounced effect upon the pituitary when given by themselves, although they tend to counteract the hypophyseal enlargement otherwise produced by folliculoids.

THYROID HORMONE causes variable changes in the anterior-lobe, although most investigators agree that a proliferation of the basophils with hypertrophy of their Golgi apparatus is rather characteristic.

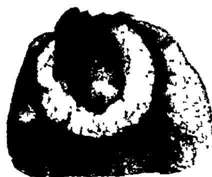
OTHER HORMONE PREPARATIONS have not been found to elicit any characteristic anterior-lobe changes.

Diseases. — In ADDISON'S DISEASE, the pituitary is usually small and the number of basophils diminished. These changes are especially conspicuous, when the adrenal insufficiency is secondary to a primary anterior-lobe failure (see. p. 263).

In juvenile DIABETES MELLITUS, the weight of the pituitary is diminished and the number of eosinophils decreased These cells also show retrogressive changes, particularly atrophy In rare instances the basophilic cells show hydropic degeneration. More often than in any other condition, foci of fetal cells, characterized by high cylindric shape, are seen in diabetes (*E. J. Kraus*).

In MYXEDEMA and HYPERTHYROIDISM, characteristic anterior-lobe lesions are not observed, although various investigators described minor changes which they consider to be typical. Usually, the anterior-lobe of patients with Graves' disease is small and the chromophils show signs of degeneration.

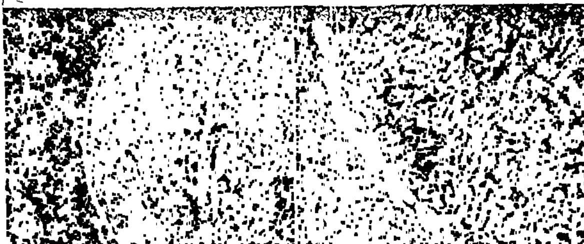
HYPERTENSION AND RENAL DISEASES are claimed to be frequently accompanied by the so-called "basophilic in-



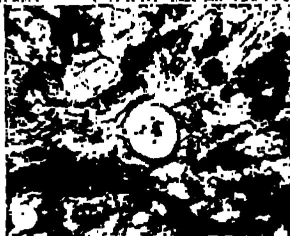
A



B







... this series (not in the one shown here) the pituitary cleft was distended with fluid — E. High magnification of a cell in mitosis taken from the posterior-lobe of the rat shown in Fig D

(After H Selye and C E Hall Anat Rec 86, 579 1943)

ing. Bilateral extirpation of the superior cervical sympathetic ganglia in rabbits has also been claimed to decrease the eosinophil count of the anterior-lobe. Some investigators believe that the cervical sympathetic may be partly responsible for the hypophyseal changes elicited by mating especially since its electric stimulation (as that of the brain or spinal cord) can cause pseudopregnancy.

Age. — Changes in pituitary weight during the course of normal life, have been discussed under "Anatomy." Histologically, basophilic invasion of the posterior-lobe is alleged to be a characteristic manifestation of senility in man. It has also been claimed that the cystic portion, corresponding to the pars intermedia, increases in old people, although its colloid content remains the same. There is a decrease in the eosinophil, and an increase in the chromophobe count, while the basophils show no significant change *(Rasmussen)*. Sometimes, lipid granules may accumulate in the anterior-lobe cells of very old people.

Sex. — In most laboratory animals, as well as in man, the anterior-lobe of females is larger than that of males. The weight of the other lobes is essentially independent of sex.

Estrus and Menstruation. — In several animal species, histologic changes characteristic of certain phases of the sexual cycle have been described; these do not lend themselves to generalizations, since they are qualitatively different in various species. In animals with a seasonal estrus, the anterior-lobe is usually largest at the height of heat.

Pregnancy. — The anterior-lobe is selectively enlarged during gestation in various species including man. Following repeated pregnancies, this growth becomes even more prominent.

In the rat, the eosinophils decrease and the chromophobes increase in number during gestation. Many large, light, "pregnancy cells" arise from chromophobes or basophils. They contain ver fine eosinophilic granules and resembl the cells which proliferate in the anterior-lobe after folliculoid hormone treatment.

In the human pituitary, no very characteristic histologic change is seen to accompany the anterior-lobe enlargement typical of gestation. It is questionable whether the disturbances of vision, often occurring in pregnant women, are due to compression of the optic chiasm by the enlarged hypophysis, or whether they result from functional disturbances.

Lactation. — In certain animals (e.g., guinea pig), almost all the eosinophils are degranulated postpartum, but in most species, the hypophyseal changes during lactation are not essentially different from those of pregnancy.

Season and Hibernation. — In animals with a seasonal estrus, and especially in hibernating animals (e.g., squirrel, wood-chuck, marmot), the weight of the anterior-lobe decreases considerably during the non-breeding or hibernating season and reaches a maximum at estrus. Concurrently, with the involution during the off-season, the chromophils lose their granules. There are no characteristic changes in the intermediate and posterior-lobes. It is probable that the above-mentioned seasonal variations are chiefly correlated with the sexual cycle rather than with hibernation in itself. However, a decreased production of corticotrophin, thyrotrophin and other metabolic anterior-lobe hormones during hibernation, is suggested by the decrease in metabolism and the atrophy of the adrenal cortex and thyroid.

Drugs. — Various drugs have been claimed to cause more or less characteristic lesions in the pituitary, but only a few of these appear to be specific.

Alloxan causes degenerative changes, ranging from hydropic degeneration to hyalinization necrosis and cyst for-



A



B





... series (not in the one shown here) the pituitary cleft was distended with fluid — E. High magnification of a cell in mitosis taken from the posterior-lobe of the rat shown in Fig D

(After H Selye and C E Hall Anat Rec 86 579 1943)

mation in the anterior-lobe of various animals. The basophils appear to be *particularly affected and there may* be some correlation between this lesion and the concurrent degeneration of the Langerhans islets which results in diabetes.

THIOUREA and its derivatives, which interfere with thyroid hormone production, cause the same type of basophil degeneration in the anterior-lobe, as thyroidectomy. Accordingly, thyroid hormone treatment prevents the pituitary lesions produced by thiourea derivatives. *In the case of complete inactivation of the thyroid by thiourea, about* 2.25γ of *dl*-thyroxin/100 *gm*. of body weight/day, is required to prevent these basophil changes in the rat. It was concluded that this represents the daily thyroid hormone requirement of the rat and that the pituitary change is indicative of an increased thyrotrophic hormone production, as part of the compensatory hypertrophy mechanism, elicited by thyroid deficiency

Feeding or intravenous injection of hypertonic NaCl solutions causes swelling of the posterior-lobe, increased mitotic proliferation of pituicytes and fluid accumulation in the hypophyseal cleft in the rat. Presumably these changes are due to the increased demand for posterior-lobe hormones occasioned by the resulting disturbance in water metabolism. (See: p 261.)

Rays. — LIGHT increases the melanophore hormone content of the amphibian hypophysis and simultaneously, elicits absorption of the intermediate-lobe colloid into the capillaries, presumably a sign of increased secretion. In mammals, neither light nor ULTRA-VIOLET rays exert any noteworthy effect upon the structure of the pituitary, although it has been claimed that in the FERRET, exposure to ultra-violet irradiation causes the appearance of large cells in the anterior-lobe, concurrently with the induction of estrus.

X-RAYS may cause complete destruction of the anterior-lobe, but usually only in doses which damage the adjacent brain centers sufficiently to cause death. In embryonic chicks, X-ray treatment of the pituitary region may completely destroy the hypophyseal primordium, so that the gland fails to develop. This is usually accompanied, however, by other severe malformations of the cephalic end of the body.

In man, the pituitary is rather sensitive to X-ray treatment and temporary castration may result from irradiation of the hypophyseal region. The therapeutic value of X-ray treatment of the pituitary in hypophyseal diseases will be discussed in conjunction with the latter.

DISEASES OF THE HYPOPHYSIS

MALFORMATIONS

Among the malformations of the hypophysis, those which tend to give rise to hormonal disturbances are comparatively rare Malformations of the cephalic end of the embryo, especially anencephaly may lead to abnormal development, and in rare instances to APLASIA, of the hypophysis In many cases of anencephaly, however, the pituitary is normal. HYPOPLASIA of the gland has repeatedly been described, even without anencephaly, in individuals exhibiting signs of the adiposogenital syndrome, dwarfism or diabetes insipidus.

In rare instances, there is DYSTOPIA OF THE NEURO-HYPOPHYSIS, that is, separation of the posterior from the anterior-lobe so that the former becomes situated above the diaphragm and is connected with the latter by a thin stalk only. The condition resembles that normally existing in some animals (e.g., whale). Lesser degrees of pituitary malformation are occasional-

ly seen in mongolian idiocy, a syndrome regarded by some as a special type of hypopituitarism.

SIMPLE ATROPHY AND SCLEROSIS of the hypophysis may result from vascular disturbances or inflammatory lesions. Sometimes it is "idiopathic," that is, due to unexplained causes. It may occur as part of the "pluriglandular dystrophy" of Falta, a syndrome in which several endocrine glands undergo sclerosis and atrophy. Probably most of the allegedly pertinent cases are actually instances of hypopituitarism with secondary atrophy of those endocrines which are under pituitary control. However, in a few cases the endocrine glands exhibit sclerosis and chronic inflammatory lesions rather than the simple atrophy seen as a result of hypopituitarism. (See also . p. 867.)



Amyloidosis of the hypophysis. [illegible] *geneous amyloid deposits which compress the anterior-lobe cell cords*

VASCULAR LESIONS

Direct trauma may cause HEMORRHAGES AND NECROSIS of the hypophysis, sometimes conducive to acute hypopituitarism. THROMBOSIS, EMBOLISM and INFARCTS of the pituitary vessels themselves or of the sinus cavernosus can likewise result in acute hypopituitarism. Bacterial emboli are often the cause of pituitary infarcts. Such vascular lesions are especially common after complicated childbirth and in such cases tend to cause the postpartum type of Simmonds' disease. (See also : p. 267.)

DEGENERATIONS

"CLOUDY SWELLING" is difficult to recognize in the pituitary and it is doubtful whether it ever occurs HYDROPIC DEGENERATION of the basophils has been described as a characteristic accompaniment of diabetes mellitus.

HYALINE DEGENERATION of the stroma may occur in the pituitary of old people as a sequel to tuberculosis, syphilis or other inflammatory lesions.

The term "COLLOID DEGENERATION" has often been used to describe the formation of colloid cysts within the anterior-lobe or at the border-line between the anterior and posterior-lobe, a region in which some small colloid cysts are normally present. Allegedly this is particularly frequent in patients with intra-cranial growths. It is doubtful whether we should refer to this as a degenerative process.

AMYLOIDOSIS of the hypophysis is extremely rare and almost always occurs as part of generalized amyloidosis.

FATTY DEGENERATION of pituitary cells may occur in cases of acute yellow liver atrophy, leukemia, phosphorus poisoning, septicemia, chronic nephritis, etc , that is to say, in diseases in which fatty degeneration of other organs is likewise common.

Among rare degenerative lesions, we might also mention the DEPOSITION OF CALCIUM, GLYCOGEN and PIGMENT GRANULES (especially hemosiderin).

INFLAMMATIONS

NON-SPECIFIC INFLAMMATORY LESIONS, usually described as "hypophysitis," may occur as a result of hematogenous infections, especially bacterial emboli, which sometimes cause abscess formation and extensive destruction of

mation in the anterior-lobe of various animals. The basophils appear to be *particularly affected and there may be* some correlation between this lesion and the concurrent degeneration of the Langerhans islets which results in diabetes.

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transition between simple hyperplasia and adenoma formation ("ADENOMATOUS HYPERPLASIA") While eosinophilic adenomas are usually limited to the anterior-lobe, basophilic adenomas are sometimes found within the substance of the pars nervosa; here basophilic infiltration of the posterior-lobe is a frequent accompaniment.

A comparatively rare, special type of the chromophobe adenoma consists of tubularly arranged, high-cylindric chief cells, not unlike those of the embryonic pituitary. Sometimes these so-called "FETAL ADENOMAS" exhibit signs of malignancy.

The ADENOMA PSAMMOSUM is an anterior-pituitary tumor whose cells are poor in cytoplasm and surround hyalinized, often calcified, concretions. Occasionally, calcification may go so far as to cause an almost bone-like hardening of the gland. All types of pituitary adenomas are more frequent in advanced age and only 6% of them are seen in individuals younger than 20 years.

PRIMARY CARCINOMAS of the anterior-lobe usually consist of wider trabeculae and more irregular cells than those of normal pituitary tissue. Yet their differentiation from adenomas is not always possible, unless malignancy is demonstrated by infiltrative growth or metastases. Intermediate types have often been referred to as "*malignant adenomas*," which is a rather confusing designation.

CYSTS of the pituitary are often lined by ciliated epithelium, such as that normally present in the "intermediate-lobe" region If sufficiently large they may cause hypopituitarism due to compression of the anterior-lobe tissue.

The CRANIOPHARYNGIOMAS or "Erdheim tumors," are probably derived from the craniopharyngeal duct. They consist of cells, similar to those of the stratum spinosum of the epidermis, which form massive cell cords Occasionally, they have a gelatinous, myxomatous stroma reminiscent of *adamantinomas* Pearl-like cornified masses are absent, but sometimes large cystic cavities (so-called pseudocysts) are formed in these tumors. Occasionally part of the tumor undergoes ossification or calcification, this may lead to confusion with teratomas, but the distinction is rather academic since the craniopharyngioma is derived from an embryonic vestige. Sometimes these growths contain a great deal of glia, bone, adenomatous tissue, pigment and cholesterol. The so-called *"cystic-papillomatous craniopharyngioma"* is a special type of this tumor; it contains large cysts, the interior of which is occupied by cauliflower-like outgrowths of stratified squamous epithelium which show a marked tendency to desquamate the superficial layers. Here again calcification and ossification of the stroma may occur.

MALIGNANT CRANIOPHARYNGIOMAS are actually basal-cell carcinomas of the craniopharyngeal duct Unlike other carcinomas they are especially common in young people, while the benign craniopharyngiomas are more frequent in adults and older patients.

CHOLESTEATOMAS are occasionally found in the region of the infundibulum, but not in the pituitary itself. Unlike the craniopharyngiomas they show kerato-hyaline pearl formation This has been considered a sign of their epidermal origin which distinguishes them from the craniopharyngiomas (arising from oral ectoderm, but not from the epidermis).

True TERATOMAS of the pituitary are supposedly rare since most of the allegedly pertinent cases of the old literature are now classed as craniopharyngiomas.

FIBROMAS, LIPOMAS, ANGIOMAS, and SARCOMAS of the hypophysis, as well as GANGLIONEUROMAS and GLIOMAS of the posterior-lobe are rare.

METASTATIC CARCINOMAS, and in very exceptional instances, SARCOMAS of the pituitary may also occur


Tuberculosis of the hypophysis. Caseous tuberculoma in posterior-lobe. Note line of demarcation between homogeneous necrotic mass and remnant of healthy posterior-lobe tissue; in this region granuloma cells predominate. Anterior-lobe and pars tuberalis are normal

pituitary tissue. Chronic inflammatory lesions with round-cell infiltrations may gradually lead to sclerosis of the hypophysis and hypopituitarism. In other instances, inflammations spread directly to the pituitary from the sinus cavernosus, the meninges or the sphenoid bone.

Among the specific inflammatory lesions, TUBERCULOSIS and SYPHILIS are noteworthy since they can cause sufficient destruction to produce hypopituitarism.

TUMORS

The clinical aspects of pituitary tumors will be discussed in connection with the hormonal disturbances they produce. Here we shall consider them only from the morphologic view-point.

Adenomas. — Pituitary adenomas of small, often microscopic, size are comparatively common; they are found in about 10% of all human pituitaries. According to the prevalent cell type, we differentiate between: CHROMOPHOBE, EOSINOPHILIC and BASOPHILIC *adenomas*. Only rarely does the same adenoma contain both eosinophils and basophils ("MIXED ADENOMAS"), or do separate eosinophilic and basophilic adenomas develop in the same pituitary. Some adenomas have no capsule and are consequently difficult to delimit from adjacent normal pituitary tissue. Hyperplastic nodules of this type form a


Eosinophilic adenoma of the hypophysis. Note dark eosinophilic cells forming adenoma which is clearly delimited from the remaining pituitary tissue (right).


Basophilic adenoma of the hypophysis. Note sharp delimitation of the irregular adenoma tissue from the normal anterior-lobe cell cords

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PRIMARY CARCINOMAS of the anterior-lobe usually consist of wider trabeculae and more irregular cells than those of normal pituitary tissue. Yet their differentiation from adenomas is not always possible, unless malignancy is demonstrated by infiltrative growth or metastases. Intermediate types have often been referred to as *"malignant adenomas,"* which is a rather confusing designation.

CYSTS of the pituitary are often lined by ciliated epithelium, such as that normally present in the "intermediate-lobe" region. If sufficiently large they may cause hypopituitarism due to compression of the anterior-lobe tissue.

The CRANIOPHARYNGIOMAS or "Erdheim tumors," are probably derived from the craniopharyngeal duct. They consist of cells, similar to those of the stratum spinosum of the epidermis, which form massive cell cords Occasionally, they have a gelatinous, myxomatous stroma reminiscent of *adamantinomas* Pearl-like cornified masses are absent, but sometimes large cystic cavities (so-called pseudocysts) are formed in these tumors. Occasionally part of the tumor undergoes ossification or calcification; this may lead to confusion with teratomas, but the distinction is rather academic since the craniopharyngioma is derived from an embryonic vestige. Sometimes these growths contain a great deal of glia, bone, adenomatous tissue, pigment and cholesterol. The so-called *"cystic-papillomatous craniopharyngioma"* is a special type of this tumor; it contains large cysts, the interior of which is occupied by cauliflower-like outgrowths of stratified squamous epithelium which show a marked tendency to desquamate the superficial layers Here again calcification and ossification of the stroma may occur.

MALIGNANT CRANIOPHARYNGIOMAS are actually basal-cell carcinomas of the craniopharyngeal duct Unlike other carcinomas they are especially common in young people, while the benign craniopharyngiomas are more frequent in adults and older patients.

CHOLESTEATOMAS are occasionally found in the region of the infundibulum, but not in the pituitary itself Unlike the craniopharyngiomas they show kerato-hyaline pearl formation This has been considered a sign of their epidermal origin which distinguishes them from the craniopharyngiomas (arising from oral ectoderm, but not from the epidermis)

True TERATOMAS of the pituitary are supposedly rare since most of the allegedly pertinent cases of the old literature are now classed as craniopharyngiomas.

FIBROMAS, LIPOMAS, ANGIOMAS, and SARCOMAS of the hypophysis, as well as GANGLIONEUROMAS and GLIOMAS of the posterior-lobe are rare

METASTATIC CARCINOMAS, and in very exceptional instances, SARCOMAS of the pituitary may also occur.

ANTERIOR-LOBE HYPOFUNCTION

DEFINITION

Anterior-lobe hypofunction is a condition in which the hormone production of the anterior-lobe is sufficiently disturbed to cause detectable manifestations of insufficiency. Among these, hypogenitalism, a decreased B.M.R. and muscular weakness are especially prominent. In young individuals this is accompanied by dwarfism; in adults by a *tendency towards the development* of cachexia.

CLASSIFICATION

The clinical types of anterior-lobe deficiency may be classified according to different viewpoints, such as the AGE OF ONSET, the intensity of the endocrine deficiency, the underlying PATHOLOGIC LESION in the anterior-lobe, etc It is most customary however, to classify these syndromes according to the CLINICAL MANIFESTATIONS which they elicit. In this sense, we distinguish

(1) *Late, general anterior-lobe deficiency (Simmonds' disease), in which* the condition develops after completion of normal growth. Since Dr Simmonds' patients suffered from severe cachexia, some authors object to the use of the term Simmonds' disease when this typical manifestation is absent. Yet we shall employ it as synonymous with "late, *general anterior-lobe deficiency*" in order to avoid this cumbersome (though more correct) designation.

(2) *Early, general anterior-lobe deficiency* (Lorain-Levi Syndrome or pituitary dwarfism) in which the onset precedes the ossification of the junction cartilages. (See also . classification of *infantilism and dwarfism, pp 286, 287.)*

(3) *Selective failure of certain anterior-lobe functions,* which is frequently due to the "shift in anterior-lobe-hormone production" elicited by a greatly increased requirement for one particular type of hypophyseal principle (e g., decreased gonadotrophin and somatotrophin *secretion* at the expense of corticotrophin such as occurs during the general-adaptation-syndrome, or after folliculoid overdosage). — *In dystrophia adiposogenitalis (Fröhlich's syndrome)* and the *Laurence-Moon-Biedl Syndrome* there is selective failure of gonadal development and adiposity without any other manifest sign of hypopituitarism. These syndromes, and perhaps even the "metabolic craniopathy" *(p. 287) probably result from* deranged gonadotrophin production, presumably caused by lesions in the vegetative centers of the hypothalamus

The word "*panhypopituitarism*" has *often been used to designate complete* failure of all anterior-lobe functions. Since *it may give rise to confusion* with *simultaneous failure of both the anterior* and the posterior-pituitary, we shall not use this designation.

PATHOLOGIC ANATOMY

Both SIMMOND'S DISEASE and PITUITARY DWARFISM may be caused by any local lesion which destroys most or all



Hypophysis in Simmonds' disease. Note almost complete replacement of hypophysis by scar tissue Only a few anterior-lobe cell groups persist (*Courtesy of Dr W Boyd*)

of the pars glandularis. Among such lesions are: tumors, hemorrhage, inflammatory processes and granulomas, hypoplasia, atrophy, etc. Among the tumors, the chromophobe adenomas and cranio-pharyngiomas are the most common cause of hypopituitarism, because they themselves are not hormone-producing. However, even eosinophilic adenomas with acromegaly, or chromophobe adenomas with Cushing's disease *may eventually result in secondary hypopituitarism, if the neoplastic tissue undergoes necrosis or extensive infarction as a result of vascular disturbances.*

FROHLICH'S SYNDROME may be unaccompanied by any detectable lesion in the hypothalamico-pituitary region, but usually there are signs of an intrasellar, or suprasellar tumor and a chromophobe adenoma or Rathke-pouch cyst is found at operation

We have no data concerning the causative anatomic lesion in the LAURENCE-MOON-BIEDL SYNDROME

INCIDENCE

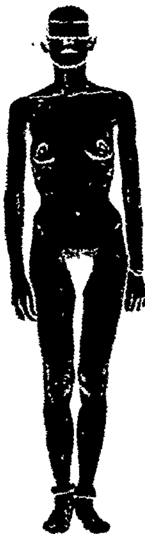
General anterior-lobe deficiency may occur at any AGE, but in children it is comparatively rarely accompanied by the profound cachexia, characteristic of late Simmonds' disease.

Mild adiposogenital dystrophy, as well as other types of selective gonadotrophin deficiency are more common in prepubertal than in older individuals, while the classic syndrome of severe adiposogenital dystrophy tends to develop in adults.

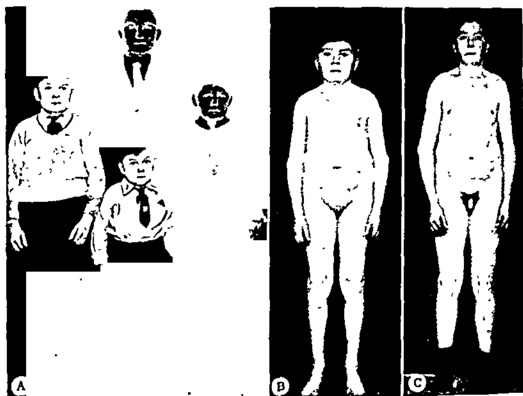
PREGNANCY definitely predisposes to Simmonds' disease, and the latter often appears immediately postpartum In such cases the causative lesion is usually a pituitary infarct (See p. 263)

Simmonds' disease is about 4 times more frequent in the female SEX, adiposogenital dystrophy is more common among boys, while the incidence of Laurence-Moon-Biedl syndrome is about equal in the two sexes

HEREDITY also plays an important rôle in the development of various hypopituitary conditions Dwarfism, combined with obvious signs of infantilism, has repeatedly been seen in families in which other members also show definitely stunted growth The hereditary occurrence of dwarfism in certain strains of mice (with aplasia of pituitary eosinophils) also indicates the importance of genetic factors. Since severe anterior-pituitary failure causes



Ovarian failure with malnutrition. 28-year-old woman with ovarian failure and malnutrition, following delivery 4 years earlier Hypomenorrhea, *vaginal smears markedly deficient,* endometrium atrophic. FSH 26-53 M.U./24 hrs., 17-KS 6 8 mg/24 hrs., visual fields normal (Postpartum Simmonds syndrome ?) (Courtesy of Dr E P McCullagh)



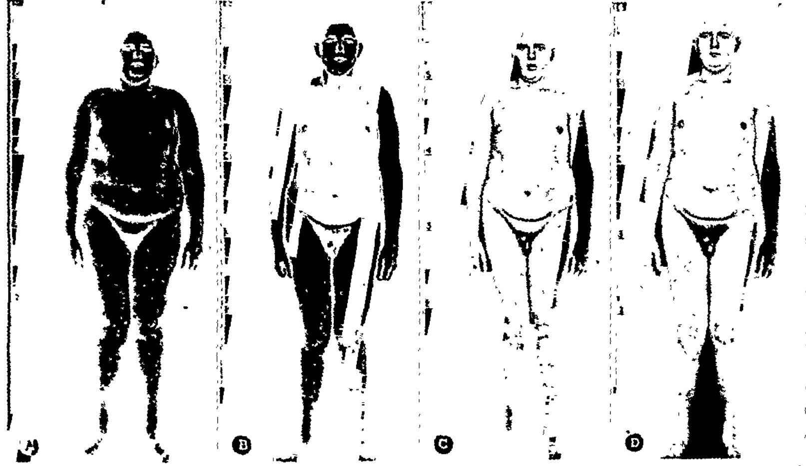
Familial dwarfism. — A. Father of normal size (5'6", weight 175 lbs). Three sons (from left to right) 25 11 and 22 years old respectively, show signs of hypopituitarism, hypothyroidism and hypogonadism Mother obese (weight 270 lbs), but of normal height (5'6"), two sisters of normal stature — B. Oldest of three brothers shown in A Note immaturity of facies, genitalia and body appearance at 25 years of age The sella and visual fields were normal Epiphyseal maturity markedly delayed Urinary gonadotrophins too low to measure, 17-KS 0 1 mg/24 hrs, BMR —35%, blood cholesterol 326 mg% — C. 5 years later Note striking maturation in appearance of face and body due to treatment with thyroid, methyltestosterone and LH (Courtesy of Dr E P McCullagh)

sterility, direct transmission of the manifest disease is rarely possible

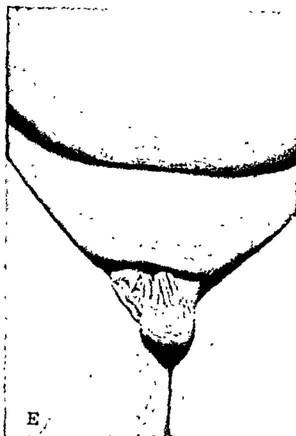
PATHOGENESIS

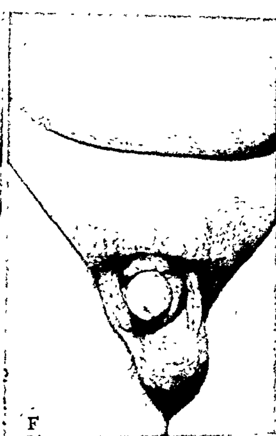
We have already discussed the ANATOMIC LESIONS found in the hypophyses of patients with anterior-lobe deficiency (see: pages 262 to 264) These destructive lesions interfere with the normal production of anterior-pituitary hormones and consequently cause derangements in metabolism as well as inhibition of growth, thyroid, adrenal-cortical and gonadal development

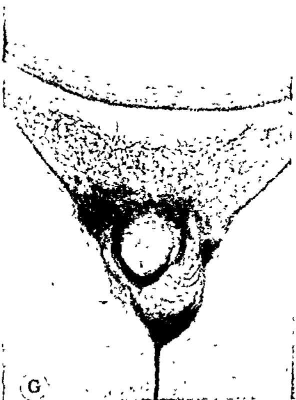
It is especially important to remember, however, that many types of anterior-lobe deficiency are due to purely FUNCTIONAL CAUSES Among these the repeatedly mentioned "shift in anterior-lobe-hormone production" is especially important. It is apparently due to an adaptive readjustment of hypophyseal-hormone secretion during periods of stress. Under such conditions somatotrophin, gonadotrophin and prolactin production are diminished, presumably in order to permit maximal elaboration of the vitally needed corticotrophin The severe cachexia and hypogenitalism of anorexia nervosa, often accompanied by a decrease in the B M R., probably also represents a special type of this protective adaptation phenomenon. Clinical evidence of pituitary failure is demonstrable in most cases of cachexia, regardless of its cause, presumably because the resulting decrease in metabolic and genital functions is advantageous under such conditions

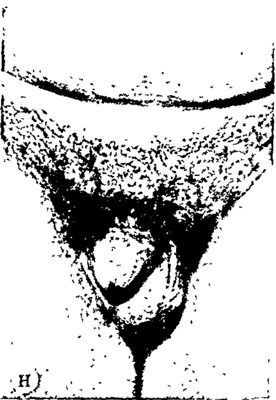


Obesity and testicular failure (adiposogenital dystrophy) without other signs of pituitary failure — A. Age 14 *years*, sella turcica normal, visual fields normal, height 68", weight 209 lbs. Penis not visible, right testis small pea size, left testis pecan size. 17-KS 2.2 mg/24 hrs. Urinary FSH repeatedly over 105 MU/24 hrs. — B, C and D, Continued improvement on chorionic gonadotrophin (LH) 500 I.U. to 750 I.U. 3 times weekly without dietary restriction (B after 9 months, C *after 13 months and* D *after* 21 months of treatment) (Cont'd.)


E


F


G


H

In adiposogenital dystrophy and in the Laurence-Moon-Biedl syndrome, the hypogenitalism is probably due to a more or less selective failure of gonadotrophin production caused by lesions in the "sexual centers" of the hypothalamus.

CLINICAL COURSE

State. — The most characteristic features of SIMMONDS' DISEASE are : loss of hair (particularly in the pubic and axillary regions), loss of teeth, trophic changes in the nails and skin (the latter is conductive to "geroderma" or "progeria" that is, the appearance of premature senility), atrophy of the genital organs (uterus, breasts, testes), amenorrhea, sterility, loss of libido, impotence, muscular weakness; a decrease in the pulse rate, blood pressure, body temperature, B.M.R. and fasting-blood sugar, mental apathy and greatly diminished sensations of hunger and thirst. Gradually profound cachexia may develop, but contrary to common opinion, this is a late manifestation of anterior-lobe insufficiency. The course of the disease is usually very slow and cases have been observed in which death did not occur until 20 years, or more, after the onset of the first symptoms.

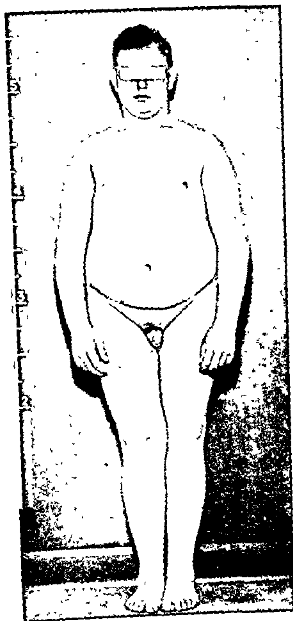
In PITUITARY DWARFISM body growth is inhibited due to a delay in the ossification of the junction cartilages. The various parts of the body retain their infantile proportions. The voice and body hair are child-like. Due to intense wrinkling of the skin, the facial expression of adult pituitary dwarfs is often suggestive of premature senility. The gonads and secondary sexual characteristics fail to develop, but cachexia is usually absent and the B M.R. may remain essentially normal. Pituitary dwarfism is often associated with adiposity, diabetes insipidus or both these conditions, perhaps because of simultaneous lesions to the hypothalamic region. The mental development of these "midgets" is normal and frequently they are even unusually intelligent and industrious. This is remarkable in view of their secondary thyroid and adrenal insufficiency.

ADIPOSOGENITAL DYSTROPHY is actually a combination of adiposity and genital dystrophy. In certain cases these two cardinal manifestations may appear at different times, thus indicat-



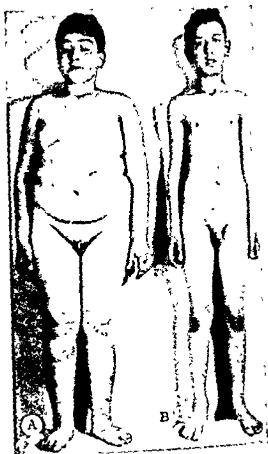
— E. Close-up of sex organs in Fig A — F. Close-up of sex organs in Fig B — G. Close-up of sex organs in Fig C — H. Close-up of sex organs in Fig D — I. After 5 months' treatment with approximately 500 I U of LH three times a week, most tubules are fairly well-developed, although spermatogenesis is not yet detectable The Leydig cells begin to proliferate

(Courtesy of Dr E P McCullagh)



Obesity. Age 15 years, height 67¾", weight 231 lbs (ideal weight 135 lbs), sella normal by X-ray visual fields normal, genital development entirely normal, urinary FSH normal The patient is shown as an example of a type frequently mistaken for Frohlich s syndrome or adiposogenital syndrome

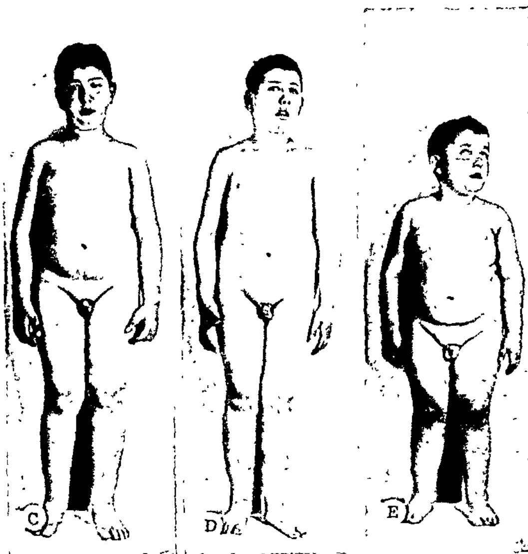
(Courtesy of Dr E P McCullagh)



(Cont'd on p 273)

ing their relative independence of each other. The gonads and secondary sex characteristics are undeveloped, the skin is delicate and often unusually white The patients may be mentally retarded but this is not always the case, although they are usually apathetic, lazy and sexually indifferent Adiposogenital dystrophy is sometimes associated with dwarfism and diabetes insipidus, presumably due to accompanying lesions of the anterior and posterior-lobe respectively, but in some cases growth is normal or even excessive

The LAURENCE-MOON-BIEDL SYNDROME is a rare type of adiposogenital dystrophy, characterized by adiposity, genital dystrophy, retardation of mental development, skull deformities, and congenital malformations such as atresia of the anus, polydactyly (formation of supernumerary fingers or toes) and retinitis pigmentosa The syndrome is hereditary, often affecting several members of the same family. Only about 90 cases have so far been described and in the absence of adequate autopsy reports the underlying pathology is not known It is probable that a congenital malformation of the hypothalamic region may be the cause of the adiposity



Familial occurrence of Laurence-Moon-Biedl syndrome. — A, B, C, D and E. Laurence-Moon-Biedl Syndrome in four of five brothers. The second boy (B) is entirely normal. The parents are first cousins. (Courtesy of Dr. E. P. McCullagh.)

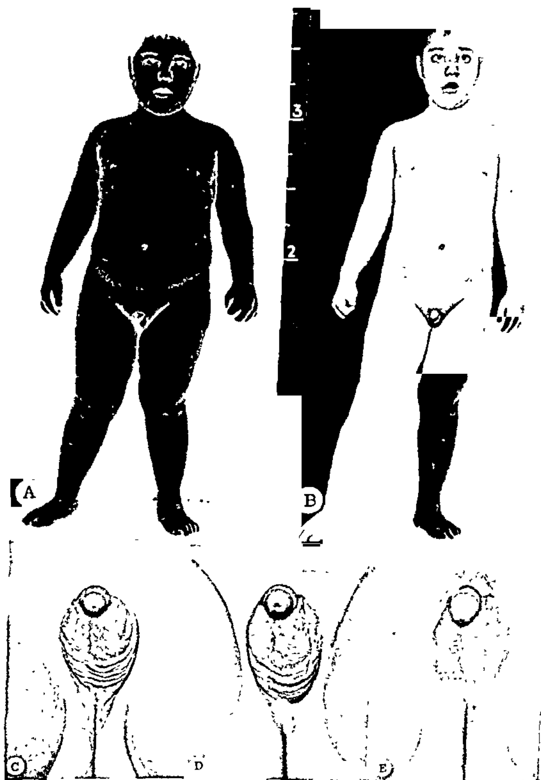
and the genital dystrophy. There is no radiologic evidence of a pituitary lesion in these patients.

In the case of SELECTIVE FAILURE OF CERTAIN ANTERIOR-LOBE FUNCTIONS there may be severe cachexia or no change in the general appearance of the patient. The latter is frequently the case in menstrual disturbances of the "pituitary type" or sterility due to decreased gonadotrophin production.

Metabolism. — All types of anterior-lobe deficiency tend to cause some (usually slight) decrease in the BODY TEMPERATURE.

The B.M.R. is always subnormal in *Simmonds disease* and in many severe cases it was found to be even lower than in grave hypothyroidism. Figures as low as —50% have been recorded.

In *pituitary dwarfism* the drop in B.M.R. is rarely severe, but the evaluation of pertinent data is difficult. It would not be rational to compare the B.M.R. of an adult pituitary dwarf with that of a child of equal size, nor



Laurence-Moon-Biedl Syndrome. — A, B, C, D and E. 5-year-old boy with obesity, mental retardation, polydactyly and retarded scrotal pigmentation Penile growth produced by local methyl-testosterone ointment (10 mg daily for 3 months) (Cont d on p 275)

(Courtesy of Dr E P McCullagh)



Note scars from removal of supernumerary fingers; patient shown on p. 274.

can one obtain standard normal values by extrapolation from healthy adult individuals taking weight or surface as a basis for comparison.

In *adiposogenital dystrophy* there is no constant diminution of the B.M.R.

Anterior-lobe deficiency also causes pronounced abnormalities of CARBOHYDRATE METABOLISM. A tendency towards pronounced fasting-hypoglycemia and a great sensitivity to insulin have been noted in Simmonds' disease and in pituitary dwarfism. In adiposogenital dystrophy this is not regularly present and indeed some patients with Frohlich's syndrome exhibit a relative insensitivity to the hypoglycemic effects of insulin and fasting.

Glucose tolerance is usually significantly increased in Simmonds' disease and pituitary dwarfism, less constantly in adiposogenital dystrophy.

FAT METABOLISM is not specifically influenced by anterior-lobe insufficiency, although in Simmonds' disease loss of fat reserves is very characteristic of the late cachectic phase. Adiposogenital dystrophy causes considerable excess storage of fat, this is probably conditioned by an increased appetite combined with the apathy and laziness char-



Laurence-Moon-Biedl's Syndrome. Note characteristic polydactylism (six toes on each foot)
(Courtesy of Dr A. Pinto Viégas.)



Hypothalamic obesity. 44-year-old man, height 77", weight 330 lbs, suffers from extreme drowsiness (patient fell asleep while this picture was taken), marked thirst (fluid intake about 5 L / day), complete impotence, sella normal to X-ray, glucose tolerance of diabetic type, urinary testoids normal, B M R, +24% (7).
(Courtesy of Dr E P McCullagh)

acteristic of these patients. Pituitary dwarfs may have normal or excessive fat depots and rarely exhibit any severe cachexia. The blood cholesterol is usually normal.

The excretion of SALT is often delayed in Simmonds' disease, as judged Simmonds' cachexia, but the N P N and blood protein concentration remain essentially normal in the various types of anterior-lobe failure.

The excretion of SALT is often delayed in Simmonds' disease, as judged by chloride tolerance tests. In patients with diabetes insipidus the subsequent development of Simmonds' disease — which may follow upon secondary involvement of the anterior-lobe — cures the polyuria and polydipsia.

Growth and Bones. — In PITUITARY DWARFISM the growth of the skeleton, the appearance of ossification centers and the second dentition are greatly delayed. Union of the junction cartilages may not occur until adulthood so that some growth may be expected from somatotrophin therapy, even if it



Hypothalamic obesity. 16 years ago patient suffered a head injury, followed by polydipsia, polyphagia, somnolence and increase in weight from 175 to 315 lbs He had one 17-year-old son, but now has complete aspermia and impotence His glucose tolerance is of the diabetic type, urinary FSH 105-212 M U /24 hrs, 17-KS 5 2 mg /24 hrs, B M R —10% There is no evidence of pituitary tumor
(Courtesy of Dr E P McCullagh)

is instituted at an age when normal growth would no longer occur. (For relationship between pituitary and other types of dwarfism see: "Diagnosis," pp. 286, 287.)

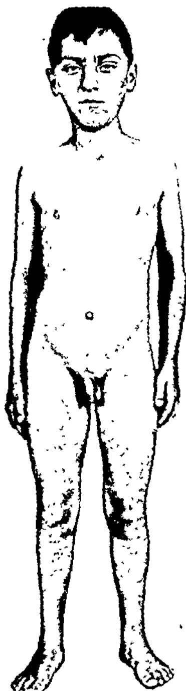
In SIMMONDS' DISEASE there is usually some osteoporosis and a tendency to lose otherwise apparently normal teeth. The latter is followed by atrophy of the jaws

ADIPOSOGENITAL DYSTROPHY may be accompanied by dwarfism, but sometimes growth in length is actually excessive. Quite frequently Fröhlich's syndrome is associated with flat feet, coxa vara and genu valgum, and patients with (pituitary?) adiposity tend to show sclerosis of the calvarium with hypoplasia of the paranasal sinuses. (See: "Metabolic craniopathy," p. 287.)

Blood. — Anemia is a constant finding in Simmonds' disease. The color index is usually less than one, and the hemoglobin averages 50%. In some instances, there is eosinophilia and lymphocytosis, but the latter are inconstant

Cardiovascular System. — Hypoplasia of the cardiovascular system and a low blood pressure are characteristic of Simmonds' disease. In pituitary dwarfism, the blood pressure may be normal and diabetes insipidus, or Fröhlich's disease may even occur in combination with hypertension (influence upon vasomotor centers of hypothalamus?). In Simmonds', as in Addison's disease, exposure to stress fails to elicit the usual pressor reaction and generally tends to cause an inverse response. Thus, even slight muscular exercise may cause a significant drop in blood pressure. This is presumably due to secondary adrenal-cortical insufficiency, since it can be prevented by suitable corticoid therapy.

Lymphatic System. — The striking hyperplasia of the thymico-lymphatic apparatus so characteristic of Addison's disease, is rarely prominent in anterior-pituitary failure. "Lymphatism" is often



Pituitary dwarfism. 16-year-old boy with deficient sexual development and growth Height 119 cm (48"), bone age corresponding to 9th year, sella normal to X-rays, no 17-KS in urine 100 mg of *testosterone propionate* weekly, during six months, caused no increase in growth rate in this case.

(Courtesy of Dr A B de Ulhoa Cintra)



[illegible] -year-old man height [illegible]

taken), marked thirst (fluid intake about [illegible] day), complete impotence, sella normal to X-ray, glucose tolerance of diabetic type, urinary testoids normal, B M R. +24% (?).

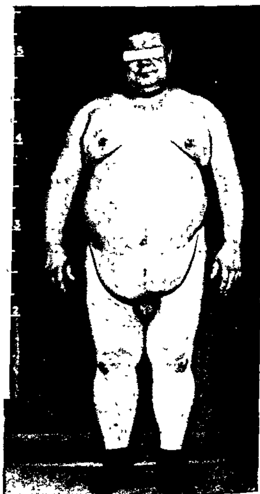
(Courtesy of Dr E P McCullagh)

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(Courtesy of Dr E P McCullagh)

conspicuous, however, with adiposogenital dystrophy.

Muscles. — The muscular system is usually atrophic, and muscular strength is considerably below normal in Simmonds' disease; to a lesser extent, this is also true of adiposogenital dystrophy and pituitary dwarfism.

Nervous System and Sense Organs. — In SIMMONDS' DISEASE, loss of libido, apathy and depression are common, while PITUITARY DWARFS are usually alert, intelligent people whose only manifestations of mental immaturity are those resulting directly from the deficient sexual development. The lack of libido and impotence may lead to serious psychologic disturbances, which are frequently aggravated by the tendency of other people to ridicule these dwarfs because of their small size and because of their sexual deficiency. In an effort to compensate for the resulting inferiority complexes, pituitary dwarfs frequently marry, usually among themselves, although of course they are always sterile and almost invariably, sexually indifferent.

The indolence characteristic of ADIPOSOGENITAL DYSTROPHY and the often severe mental defects which accompany the LAURENCE-MOON-BIEDL SYNDROME have already been mentioned.

Visual disturbances are very characteristic of all hypopituitary conditions in which a disease process exerts pressure upon the optic chiasm. Usually there is bitemporal hemianopsia which sometimes develops from a central scotoma and often ends in complete blindness Similar visual defects are seen in association with the tumors which give rise to hyperpituitarism. (See : p 283.)



Simmonds' disease. — A. and B. 37-year-old woman who developed amenorrhea, loss of pubic and axillary hair, loss of weight and weakness immediately after her fourth delivery. She had a low B M R, low serum Na and Cl, high serum K, positive Robinson, Power and Kepler test, high blood cholesterol, urinary gonadotrophins and 17-KS close to 0

(Courtesy of Dr A B de Ulhôa Cintra)





Dwarfism with hypogonadism. — A Patient at 18 years of age before institution of therapy (height 49") . B Patient at 26 years of age. He received one ye

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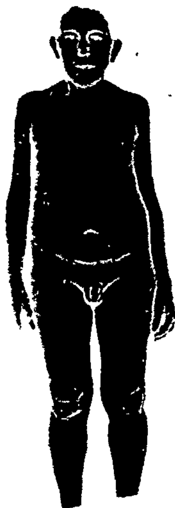
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Patient at 29 years of age Methyl-testosterone therapy was continued until 9 months before this picture was taken After this, therapy was changed to testosterone propionate in doses of 25 mg three times a week intramuscularly Height now 56" Note also maturation of facial expression, genital and muscular development, approximating those of normal adult males
(Courtesy of Dr E P McCullagh)

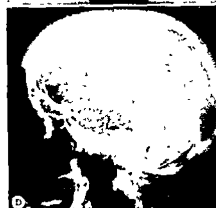


Pituitary dwarfism. On the left, a normal boy, age 15 years, weight 53 Kg (103 lbs), height 154 cm (61 inches) On the right, 15-year-old boy, with anterior-pituitary deficiency Weight 19 Kg (46 lbs), height 114 cm (46 inches). Note also deficient development of the penis and lack of pubic hair The measurements of this patient roughly correspond to those of a normal boy, age 5½-6 years (Courtesy of Dr A Pinto Viegas)









Hypopituitarism. — A. — B. — C. 44-year-old patient with signs of gonadal and adrenal deficiency Complaints were physical and mental fatigue. Note [illegible]

testosterone + desoxycorticosterone therapy — D. Skull X-ray shows marked enlargement of sella with thinning of its walls and partial erosion of the clinoid processes There is evidence of calcification, probably in the pituitary tumor or cyst wall

(Courtesy of Dr E P McCullagh)









Severe anterior-pituitary deficiency with pituitary adenoma. — A 16-year-old boy with emaciation pallor arterial hypotension (90/75) dry skin mild *polydipsia and polyuria, slight* enlargement of the sella B M R —38% 17-KS 0 7 mg /24 hrs, urinary FSH 6 M U /24 hrs, — B Two *months* following removal of pituitary adenoma X-Ray treatment to pituitary (2 000 *r a* to each temple), and 500 I U of LH three times weekly Genital and somatic development greatly improved — C Testis biopsy before treatment Note marked hyalinization of tubules and almost complete disappearance of tubular and interstitial cells — D Testis biopsy after therapy Note proliferation of both tubular and Leydig cells spermatogenesis not yet *in* progress
(Courtesy of Drs R W Schneider and E P McCullagh)

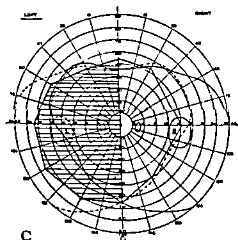
axillary hair development in conjunction with the deficient sexual development are of great diagnostic value. A very pronounced decrease in urinary 17-KS, folliculoids, corticoids and gonadotrophins is likewise typical of anterior-lobe failure.

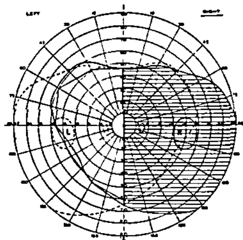
The great insulin-sensitivity of patients with Simmonds' disease has also been recommended as a diagnostic measure. However, it is dangerous, since fatal hypoglycemia may ensue after very small doses, and it is not characteristic, since in Addison's disease, anorexia nervosa, hepatic disease and many other types of cachexia, insulin-sensitivity is likewise increased.

Differentiation from ANOREXIA NERVOSA is particularly difficult. In the latter condition the fundamental cause of the symptoms is a secondary hypopituitarism and hence the manifestations are essentially the same as in Simmonds' disease. However, in anorexia nervosa, psychogenic factors are the cause of the decreased food intake and the resultant cachexia. Correspondingly, the patients are amenable to adequate psychotherapy, in conjunction with an increased









Pneumo-ventriculogram in a patient with pituitary tumor. — A. Appearance of the cerebral ventricles after air insufflation in a normal individual. Note normal position of the (dark) lateral ventricles visualized by air insufflation, also normal appearance of sella. — B. 52-
old woman
with pronou
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lost or impaired in shaded territory.

(Courtesy of Montreal Neurological Institute.)

Digestive System. — Deficient secretion of gastric and pancreatic juice are rather characteristic of Simmonds' *disease and subnormal development of* all the abdominal organs forms part of *the typical "splanchnomicria"* of anterior-lobe failure.

Skin. — The loss of hair, especially the loss of axillary and pubic hair is extremely characteristic of Simmonds' disease. Sometimes it is accompanied by loss of eyebrows. Histologically, the skin reveals atrophy of both hair follicles and sweat glands. Cutaneous pigmentation is comparatively rare in Simmonds' disease: when it occurs, differentiation from Addison's disease may become very difficult.

In adiposogenital dystrophy, absence of body hair is likewise characteristic, especially if the condition develops before puberty.

Accessory Sex Organs. — Atrophy or hypoplasia of the accessory sex organs is a constant characteristic of Simmonds' disease, pituitary dwarfism and adiposogenital dystrophy. In women there is complete amenorrhea, the uterus, vagina and breasts are atrophic and in the ovaries there is no follicle maturation, ovulation or corpus luteum formation. In men, there is atrophy of the testes and seminal vesicles, sometimes accompanied by complete absence of the prostate. Sterility in both sexes is a constant characteristic of all fully-developed cases of Simmonds' disease, pituitary dwarfism and adiposogenital dystrophy. (For relationships between pituitary and other types of genital infantilism see: "Diagnosis," below.)

Pregnancy and Lactation. — As previously stated, Simmonds' disease often occurs as a sequel to pregnancies which are followed by complicated deliveries. Since complete anterior-lobe failure is always conducive to sterility in both sexes, pregnancy and lactation do not occur in fully-developed cases of Simmonds' disease, pituitary dwarfism or adiposogenital dystrophy. The alleged *instances of fertility* among (male or female) pituitary dwarfs are due to confusion with "primordial" dwarfism or with achondroplasia (see pp 256, 287).

COMPLICATIONS

One of the most important complications of severe anterior-lobe deficiency is fatal hypoglycemia due to prolonged fasting or exposure to stress. Slight intercurrent diseases may elicit unduly serious complications or even death in these patients whose adaptive mechanism is severely deranged.

Other complications may be due to the causative pituitary lesion itself (e.g., visual disturbances, hemorrhages from pituitary tumors, increased intra-cranial pressure or invasion of the adjacent hypothalamic nuclei by hypophyseal growths).

DIAGNOSIS

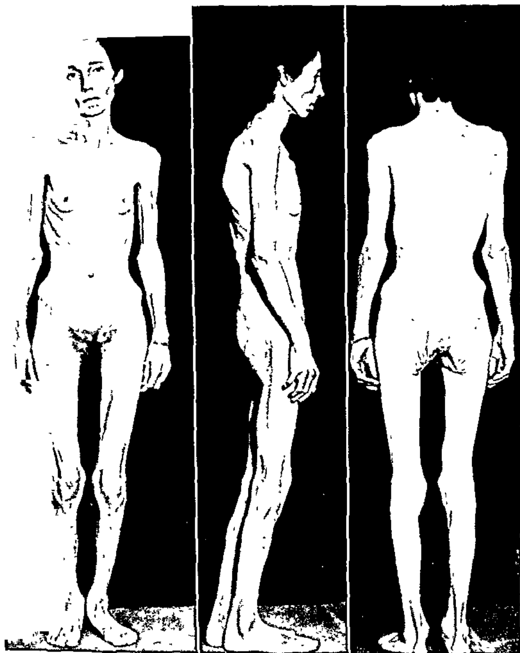
Manifestations Characteristic of Pituitary Lesions in General. — The so-called "pituitary headache" is usually most intense between the temples, deep behind the eyes and is almost invariably due to the pressure of a pituitary growth.

Other characteristic local signs are the bitemporal hemianopsia and radiologic evidence of a lesion in the pituitary region (erosion or unusual smallness of the sella, calcification in a suprasellar tumor). Signs of marked intracranial pressure develop only in the presence of extensive pituitary growths.

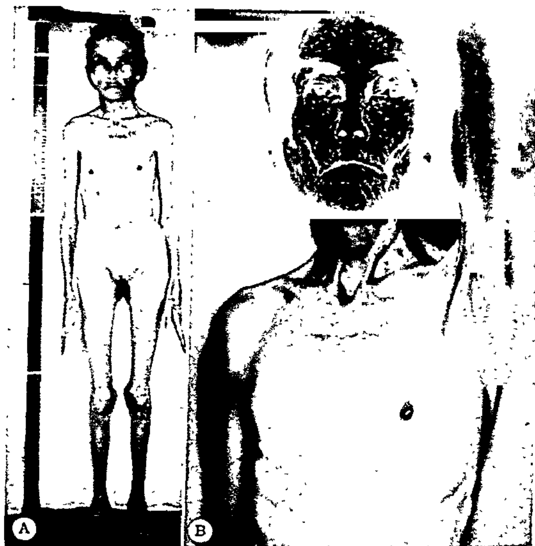
Simmonds' Disease. — Fully-developed cases of Simmonds' disease are readily recognized on the basis of the above-mentioned characteristic manifestations. On the other hand, the diagnosis of incipient or very mild instances of anterior-pituitary failure may be extremely difficult and usually requires a great deal of clinical experience. In such instances, the peculiar waxy color of the skin, the sparse beard, genital and

Differentiation from PERNICIOUS ANEMIA is rarely difficult if this condition is kept in mind.

Pituitary Dwarfism. — At birth, patients with pituitary dwarfism are usually of normal size and appearance, but later they show an inhibition in development which is inversely proportional to the age at which their anterior-lobe became deficient. The diagnosis is rarely difficult on the basis of the characteristic hormone-deficiency manifestations



Anorexia nervosa Age 34 years, height 60", weight 59 lbs X-ray of sella, chest, stomach, duodenum and colon normal, B M R —20% Ewald meal and blood counts normal, water excretion tests normal, insulin tolerance low, glucose tolerance curves flat, as in hypopituitarism Note great resemblance to Simmonds' disease (Courtesy of Dr. E. P McCullagh)



Anorexia nervosa. — A. and B. 60-year-old woman with severe emaciation due to anorexia. Mental depression, loss of axillary and pubic hair, inexpressive face. 17-KS excretion normal. Marked improvement and gain in weight was accomplished with 10 mg of methyl-testosterone/day. (Courtesy of Dr E. B. del Castillo.)

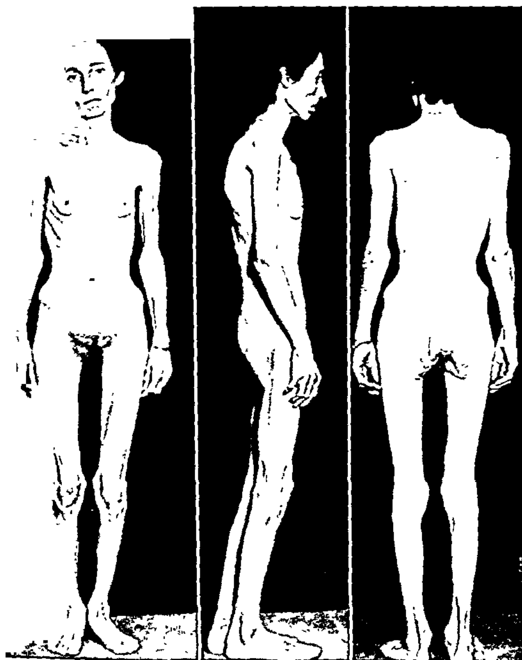
dietary intake and thyroid administration to raise the B.M.R. Edema of the legs (unrelated to the level of the serum proteins) and a great delay in the excretion of orally-administered water are likewise characteristic. There is amenorrhea of the hypopituitary type that is unaccompanied by menopausal disturbances. The urinary excretion of 17-KS is low, but not as low as in Simmonds' disease where it is practically nil.

Confusion with MYXEDEMA may occur because of the pallor, intolerance to cold, decreased B.M.R. and apathy characteristic of both these conditions. However, in hypothyroidism, the skin is coarse and dry and there is no great loss of beard, pubic or axillary hair. Hypercholesterolemia and myxedematous infiltrations are absent in most cases of Simmonds' disease.

Differentiation from ADDISON'S DISEASE may be impossible in the absence of local signs in the pituitary or adrenal region. However, pigmentation of the skin is exceptional in Simmonds' disease and the blood-electrolyte changes, characteristic of cortical insufficiency if present, are much less pronounced.

Differentiation from PERNICIOUS ANEMIA is rarely difficult if this condition is kept in mind.

Pituitary Dwarfism. — At birth, patients with pituitary dwarfism are usually of normal size and appearance, but later they show an inhibition in development which is inversely proportional to the age at which their anterior-lobe became deficient. The diagnosis is rarely difficult on the basis of the characteristic hormone-deficiency manifestations



Anorexia nervosa. Age 34 years, height 60", weight 59 lbs. X-ray of sella, chest, stomach, duodenum and colon normal, B.M.R. —20%. Ewald meal and blood counts normal; water excretion tests normal, insulin tolerance low; glucose tolerance curves flat, as in hypopituitarism. Note great resemblance to Simmonds' disease. (Courtesy of Dr. E. P. McCullagh.)

(see above) and the local signs in the pituitary region; the latter, however, are not always demonstrable.

From a differential diagnostic viewpoint, it is important to distinguish pituitary dwarfism from other types of growth inhibition and delayed psychic and genital maturation.

The term "INFANTILISM" has been used to designate conditions in which the child-like characteristics of body and psyche persist during adult life. It is well to remember however, that there is no disease which leads to the persistence of perfectly normal child-like somatic and psychic characteristics Only some of the individual's features are truly child-like, hence perfect instances of "infantilism" do not exist.

In view of the very voluminous and confusing pertinent literature, the subject deserves some discussion. Certain authors placed special emphasis upon the retardation of genital development, but if this were taken as a sign of infantilism, adiposogenital dystrophy, eunuchoidism, eunuchism and even acromegaly (when accompanied by genital dystrophy) would have to be classified under this heading Others take the stunting of somatic growth as the chief criterion, but in this sense all types of dwarfism (e g., primordial dwarfism, renal rickets, and perhaps even achondroplasia would have to be classified under the same heading)

Even if we limit ourselves to those types of "infantilism" in which both the general somatic and sexual development are delayed, the following types must be recognized:

(1) *Pituitary infantilism* (Synonyms: nanosomia infantilis, Lorain-Levi syndrome), which has been described under a variety of names, depending upon the comparative conspicuousness of certain somatic or psychic manifestations. It is now generally accepted that all these types are due to a primary anterior-lobe failure.

(2) *Brissaud's infantilism* (Synonym. hypothyroid infantilism), which is identical with hypothyroid cretinism. The mental and somatic development are retarded, but sexual maturation is less markedly impeded.

(3) *Herter's infantilism* (Synonym, intestinal infantilism) with retardation of somatic and sexual development due to some chronic gastrointestinal disease

(4) *Paltauf's infantilism* is essentially identical with "status thymico-lymphaticus" accompanied by sexual retardation.

(5) *Pancreatic infantilism*, in which the retardation of somatic and sexual development are due to pancreatic disease.

(6) *Renal infantilism* or renal rickets with stunted somatic growth and sex development.

(7) *Other types of infantilism* associated with hereditary syphilis, malaria, tuberculosis, various types of intoxication (lead, mercury), malnutrition, etc In all these cases, secondary pituitary failure is probably the causative agent Just as anorexia nervosa may produce secondary anterior-lobe deficiency in adults, thus, non-specific stress can cause hypopituitarism with "infantilism" if it elicits a general-adaptation-syndrome during childhood.

For purposes of classification and differential diagnosis it suffices to distinguish the primary pituitary dwarfism (Lorain-Levi type) from secondary anterior-lobe failure due to a variety of stresses. The former can be differentiated from the latter by the absence of manifestations indicative of the specific diseases which tend to produce secondary anterior-lobe failure (e g. hypothyroidism, infections, intoxications, and renal, cardiac or pancreatic disease).

All the above-mentioned types of "infantilism" are associated with growth inhibition, but there are other types of DWARFISM which differ from "infantilism" inasmuch as sexual development is not impeded. Among these we may mention:

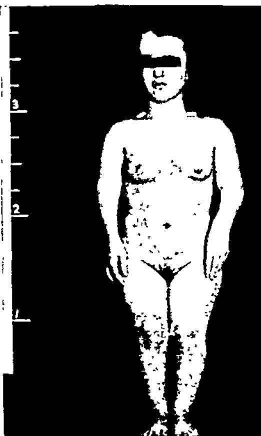
(1) *Primordial dwarfism* (Synonyms: nanosomia essentialis, primary

dwarfism, pygmyism) which differs from pituitary dwarfism in that the individual is abnormally small even at birth (since the condition is apparently due to a congenital deficiency) while pituitary dwarfism develops later in life. The genital organs of primordial dwarfs are essentially normal, the body proportions of the adult type and the ossification of the function cartilages occurs at the normal age. Their psychic development is also normal even with respect to the sexual impulses and they are capable of normal reproduction, frequently transmitting the dwarfism to their children.

(2) *Achondroplasia* (Synonym: chondrodystrophia fœtalis) is a congenital, sometimes hereditary, disease. It is presumably due to a disturbance in endochondral ossification — especially of the long bones and the base of the skull — caused by connective tissue invasion from the periosteum into the growth cartilages. These individuals are dwarfs only because their extremities are too short. Their trunk and head is of normal size, but due to the disturbance of bone growth at the base of the skull, the nose is flat and the lower jaw comparatively prominent. The hands are stubby and the fingers of equal length. The sex organs are normal and indeed, often precociously developed. The intellect is not affected.

The differentiation of these two types from pituitary dwarfism is simple, since unlike the latter they are not accompanied by genital dystrophy.

Adiposogenital Dystrophy. — It may be extremely difficult, or even impossible to differentiate adiposogenital dystrophy from EUNUCHOIDISM due to primary gonadal diseases, unless local signs call attention to the presence of a lesion in the pituitary or gonadal region. If the disease is due to some hypothalamic injury, an accompanying diabetes insipidus may help the diagnosis since other types of hypogonadism are not accompanied by polyuria



Achondroplasia. Achondroplasia in a 16-year-old girl with amenorrhea. All epiphyseal centers about the elbow and hand are fused, but those at the wrist are not yet completely ossified. Unlike in pituitary dwarfism, the growth is disproportionate (the extremities being far too short for the trunk and head), sexual development is normal (Courtesy of Dr E P McCullagh)

Confusion with the so-called METABOLIC CRANIOPATHY (Morgagni's or Stewart-Morel's syndrome) is likewise possible. This is a comparatively common, often familial, disease among middle-aged women. It is characterized by obesity, hypertension, secondary amenorrhea, hirsutism, neuropsychiatric disturbances and cancellous bone deposition on the lamina interna of the skull. It may be due to a hypothalamic disorder.

PROGNOSIS

The prognosis of SIMMONDS' DISEASE is extremely grave. However, patients may survive, in a condition of severe anterior-lobe failure for several years

and even decades if they are protected against all types of stress and if they can be persuaded to take adequate nourishment and therapy.

PITUITARY DWARFISM shows no tendency towards spontaneous improvement, but is compatible with a normal, and even a very long, active life. One such patient died at the age of 91 years. The fact that many pituitary dwarfs die early is merely due to their lack of resistance to such intercurrent stresses as infections, intoxications, etc.

ADIPOSOGENITAL DYSTROPHY due to anatomic lesions in the hypophyseo-hypothalamic region, and the LAURENCE-MOON-BIEDL'S SYNDROME likewise fail to regress spontaneously, but considerable improvement or even cures may be obtained in the former condition upon removal of the causative lesion (e.g., a craniopharyngioma). Flaccid, fat boys with "Fröhlich's Syndrome" often revert to normal at puberty without any treatment, but in such cases the causative derangement is apparently only functional.

THERAPY

Simmonds' Disease. — The logical therapy of Simmonds' disease would be substitution therapy with ANTERIOR-PITUITARY-HORMONES. Unfortunately, pure, active preparations of this type are not yet available in adequate amounts to make such treatment generally applicable. Treatment with TESTOIDS (to induce protein anabolism) or CORTICOIDS (to compensate for the secondary cortical insufficiency) has often been successful. THYROID therapy (to compensate for the secondary hypothyroidism) is dangerous, since hypopituitary patients are extremely sensitive to thyroid-hormone overdosage.

Under present conditions, the most important therapeutic measures are protection of the patient from any intercurrent disease or other types of stress (e.g., cold, emotional upset, infections), since these are likely to elicit a fatal hypopituitary crisis due to lack of adaptability.

Pituitary Dwarfism. — In pituitary dwarfism the therapy is essentially the same as in Simmonds' disease. ANTERIOR-LOBE EXTRACT or TESTOSTERONE administration has been recommended by some, not only to cause nitrogen retention and accelerate growth, but also to develop the sex organs. It is doubtful, however, whether the artificial induction of sexual maturity is desirable in these individuals. The awakening of a dormant libido may cause serious psychologic disturbances in dwarfs whose libido is rarely reciprocated.

Adiposogenital Dystrophy. — If the disease is due to a specific and anatomic lesion, such as a craniopharyngioma, SURGICAL removal of the tumor is necessary, especially if there is any danger of pressure upon the optic chiasm. Otherwise, treatment with pituitary GONADOTROPHINS or with TESTOSTERONE in males and with FOLLICULOIDS in females may be useful, especially if combined with reduction of food intake and with muscular exercise to cause loss of body weight. It is important to keep in mind however, that many adipose boys with genu valgum, flat feet and the "Fröhlich type of habitus" do not suffer from organic, hypothalamic or pituitary lesions, as their sex organs are actually normal, though hidden in the adipose tissue. In these cases, dietary restrictions and exercise alone may suffice to improve the condition; indeed at the time of puberty, such patients often become normal without any treatment.

POSTERIOR-LOBE HYPOFUNCTION (DIABETES INSIPIDUS)

DEFINITION

In principle, posterior-lobe hypofunction would be a condition in which the hormone production of the posterior-lobe is sufficiently disturbed to cause detectable manifestations of insufficiency.

In practice, only diabetes insipidus has been proven to result from such a derangement, although certain dystocias (difficult child-births) have been ascribed to uterine inertia due to a deficient oxytocin production.

CLASSIFICATION

As in the case of other endocrine diseases, diabetes insipidus may be classified according to various criteria, from a CLINICAL view-point it is most customary however, to distinguish:

(1) *Primary or idiopathic diabetes insipidus* in which the underlying cause cannot be determined.

(2) *Secondary or symptomatic diabetes insipidus* in which some organic disease of the brain and particularly of the hypothalamus (fracture of the base of the skull, basilar meningitis, pituitary or suprasellar tumors, chronic encephalitis) interfere with the hormone production of the posterior-lobe.

Some investigators like to classify diabetes insipidus according to the BLOOD CHLORIDE level into three groups

(1) *Hyperchloremic.*
(2) *Hypochloremic*
(3) *Normochloremic.*

It is claimed that in the hyperchloremic type, posterior-lobe extracts are especially effective in decreasing the polyuria and thirst while they increase the specific gravity of the urine Furthermore, allegedly in such patients, salt-poor diets are beneficial while theophylline has little effect. Conversely, in the hypochloremic and normochloremic types, posterior-lobe extracts or salt-poor diets are often almost ineffective while theophylline causes marked hyperchloruria However, this distinction is not generally recognized since some hypochloremic cases respond well to posterior-lobe extract and the blood chloride level of the same patient may at times be below, and at other times above normal

According to their SENSITIVITY TO POSTERIOR-PITUITARY EXTRACTS it has also been customary to distinguish .

(1) *Vasopressin-sensitive cases.*
(2) *Vasopressin-resistant cases.*

Anatomic studies suggest that usually, in the former, the tuberal nuclei are intact, while in the latter, they are destroyed by some local lesion.

PATHOLOGIC ANATOMY

Diabetes insipidus may result from any lesion which destroys (selectively or in combination) the posterior-lobe, the supra-optic nuclei of the hypothalamus or the stalk of the pituitary. Primary or secondary tumors (often craniopharyngiomas), inflammatory diseases (especially basilar meningitis, chronic encephalitis and syphilis), xanthomatosis, pellagra, trauma to the pituitary region, etc., may be the immediate cause of a secondary or symptomatic diabetes insipidus Nevertheless, as previously mentioned in several carefully examined cases, no anatomic lesion was detectable either in the pituitary or the hypothalamus of otherwise typical instances of diabetes insipidus. These have been regarded as due to functional derangements and are referred to as the "primary" or "idiopathic" form

INCIDENCE

Diabetes insipidus is a comparatively rare disease. Young people are most often affected and heredity appears to play an important rôle in some familial cases

PATHOGENESIS

We have already discussed the ANATOMIC LESIONS which may elicit diabetes insipidus To recapitulate, any lesion destroying the supra-optic nuclei, the tuber cinereum, the stalk or the posterior-lobe itself causes degeneration of all these structures, due to both retrograde degeneration of the neurons and peripheral degeneration of the nerve fibers together with the posterior-lobe which they supply.

The FUNCTIONAL MECHANISM through which posterior-lobe hormones (presumably vasopressin) act upon water metabolism has been discussed (*see:*

pp. 219 and 238) above. Since in the vast majority of the cases, posterior-lobe preparations exert a curative effect upon the polyuria of diabetes insipidus, it is reasonable to assume that the disease is due to a specific derangement in the production of such principles

Suffice it to reiterate here that complete destruction of the anterior-lobe inhibits the development of diabetes insipidus irrespective of the presence or absence of lesions in the supra-optico-hypophyseal system, hence the anterior-lobe presumably produces some diuretic principle. Thirsting does not prevent the polyuria so that the latter must be regarded as primary and not merely a consequence of increased water intake.

CLINICAL COURSE

The most characteristic features of diabetes insipidus are : the excretion of large quantities of pale URINE with a "fixed" low specific gravity (that is, one which remains low even when fluid intake is restricted), decreased production of sweat and saliva and occasionally marked dryness of the skin, malaise, constipation and headaches.

The B.M.R. is usually normal, but there may be HYPOTHERMIA, due to interference with hypothalamic thermoregulation. There is no specific and characteristic derangement in carbohydrate, fat and protein metabolism, although the combination of diabetes insipidus with adiposogenital dystrophy (due to lesions in adjacent hypothalamic areas) is rather common

As previously mentioned the blood CHLORIDE values may be normal, high or low. There is no strict correlation between the blood and urinary chloride concentration. It has been claimed that in the so-called "hyperchloremic-hypochloruric diabetes insipidus" there is a specific disturbance in the chloride-concentrating power of the kidney, while in the "hypochloremic-hyperchloruric cases" the renal chloride concentration is comparatively great. In the former type the urine volume is allegedly increased to help "wash out" chlorides, while in the latter, the excessive excretion of chlorides would carry the water with it.

The chloride concentration in the urine is usually markedly increased during the water retention induced by posterior-pituitary extract treatment, and this is especially evident in the hyperchloremic cases.

Diabetes insipidus is not conducive to any OTHER CHARACTERISTIC MANIFESTATIONS, except the difficulties of childbirth often (but not invariably) noted in women suffering from this disease These dystocias are ascribed to derangements in oxytocin secretion

The only important COMPLICATIONS of diabetes insipidus are those due to the local destructive effect of the causative lesion and those which may result from severe dehydration, if adequate amounts of water are not available to the patient.

DIAGNOSIS

In typical cases the diagnosis of diabetes insipidus is comparatively simple, although only LOCAL SIGNS can help to recognize the nature of the causative lesion (tumor, trauma, etc.).

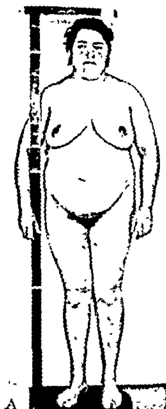
Differentiation from HYSTERIC POLYDIPSIA tends to cause the greatest difficulty. Some nervous individuals take enormous amounts of water as a result of psychic disturbances and this of course also causes marked polyuria. In this connection it is important to remember that in diabetes insipidus the specific gravity of the urine does not exceed 1.005-1.007, even if water is withheld for as long as the patient can endure it. In hysteric polydipsia, on the other hand, the specific gravity rises over 1.012 upon prolonged thirsting. The usually very marked anti-diuretic effect of vasopressin likewise helps to recognize true diabetes insipidus.

Differentiation from DIABETES MELLITUS causes no difficulty since in the latter the polyuria is always accompanied by glucose elimination in the urine.

RENAL INSUFFICIENCY with polyuria, is easily recognized by specific signs of kidney failure.

Diabetes insipidus with galactorrhea. — A. — B. and C. 33-year-old woman in whom obesity, pain in the bones, polydipsia, polyuria, headaches, diplopia, bitemporal hemianopsia acne, hirsutism, insulin resistance and bilateral galactorrhea had developed 4 years ago. Urinary 17-KS 42 mg/24 hrs., B.M.R. normal. There is radiologically demonstrable enlargement of the sella. Pitressin decreases urine output. Following removal of an, apparently chromophobe, anterior-lobe adenoma, the vision became normal within 6 days. Presumably a case of diabetes insipidus with atypical Cushing's syndrome.

(Courtesy of Dr. E. B. del Castillo.)



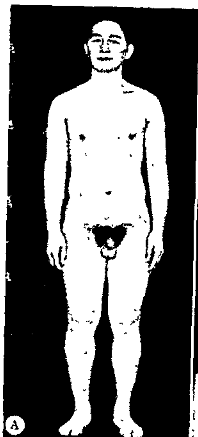
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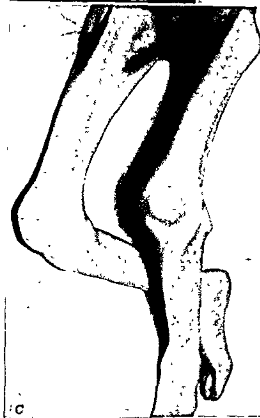
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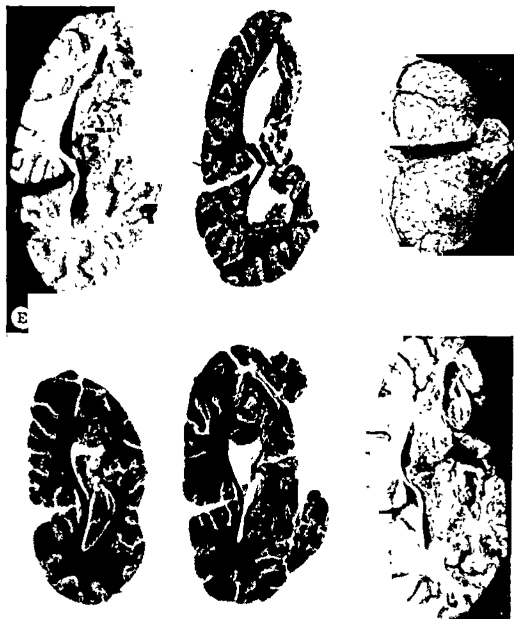








(Cont'd 3)



Diabetes insipidus progressing to Simmond's disease. — A. and B. Man, age 25 years, who suffered from diabetes insipidus during 27 months At first his nutrition was good — C. and D. As the disease progressed, there was loss of libido and potency, drowsiness, anorexia, arterial hypotension, progressive weakness and loss of weight B M R —46%, 17 KS 1 1 mg /24 hours, urinary FSH less than 6 M U /24 hrs The visual fields were normal and the sella showed no change upon X-ray examination — E. and F. Tumor (pinealoma) invading the pituitary and hypothalamus In this patient diabetes insipidus curiously persisted even after destruction of anterior-lobe (Courtesy of Dr E P McCullagh)

PROGNOSIS

Spontaneous recovery from diabetes insipidus is most common if the derangement is caused by infectious diseases or trauma, it occurs especially frequently in children. Otherwise the derangement is usually permanent and tends to become worse unless the lesions spread to the pars distalis and secondary anterior-lobe deficiency inhibits the polyuria.

Temporary improvement during the period of posterior-pituitary extract treatment is the rule, except in the rare vasopressin-resistant cases.

THERAPY

The therapy should be directed against the causative anatomic lesion whenever possible: this means removal of tumors from the hypothalamo-pituitary region, anti-syphilitic therapy when the disease is caused by syphilis, etc. In all other instances purely symptomatic treatment with POSTERIOR-PITUITARY SOLUTION (0.5-10 U.S.P units subcutaneously) generally alleviates the polyuria for a period of 6-18 hours Most patients require about 1 cc. of the official preparation, given by hypodermic injection two to three times a day.

PITRESSIN TANNATE in oil may be used in doses of 3-5 pressor units injected intramuscularly every 36-48 hrs., since it is more slowly absorbed and hence longer-acting than the aqueous solution.

Following hypodermic or intra-muscular injection, the local vasoconstrictor effect of the hormone frequently leads to unpleasant complications, hence many physicians prefer to administer pitressin on cotton pledgets soaked with the solution and APPLIED TO THE NASAL MUCOSA. Insufflation, by a spray (or atomizer) of posterior-lobe powder or aqueous pitressin preparations into the nasal cavity is likewise recommended. If dry posterior-lobe powder is to be used 50-65 mg. are placed on a piece of paper rolled in the form of a cylinder and placed into the nostril in order to aspirate it. This procedure generally has to be repeated two to four times daily. The powder may also be blown into the nose with an atomizer through a glass tube.

In the case of overdosage there may be : edema, convulsions, headache, abdominal cramps, diarrhea and sometimes even severe shock. All these symptoms are less likely to occur following *nasal, than following subcutaneous* or intra-muscular administration If they occur, injection of a mercury diuretic is indicated as an antidote.

AMINOPYRINE (15 grains or 1 gm.) one to three times daily often helps to decrease the requirements for posterior-pituitary extract Aminopyrine (and other drugs which act upon the hypothalamus) may also prove effective in certain cases which are resistant to the posterior-pituitary solution.

Furthermore, in order to decrease the reabsorptive work of the kidney it is advisable to LIMIT THE SALT INTAKE.

ANTERIOR-LOBE HYPERFUNCTION

DEFINITION

Anterior-lobe hyperfunction is a condition in which the hormone production of the anterior-lobe is sufficiently augmented to cause detectable manifestations of hyperpituitarism. Among these are the increase in the size and function of those endocrines (adrenal-cortex, thyroid, gonad) which are under anterior-lobe control. The hyperthyroidism and hypergonadism of pituitary origin have already been discussed in the chapters on the thyroid and gonads respectively, while increased

adrenal-cortical function has been considered in connection with the Cushing's syndrome of adrenal-cortical origin (see: p. 162). This disposition of the material was adopted because in pertinent cases it is often impossible to differentiate between disorders due to a primary, pituitary disease and those resulting from "idiopathic" hyperfunction of the thyroid, gonads or adrenals.

In the present section, chief emphasis will be placed upon HYPOPHYSEAL GIGANTISM, ACROMEGALY and CUSHING'S DISEASE since these syndromes are comparatively clear-cut clinical entities. In view of the frequent overlap in the symptomatology of the various clinical types of anterior-lobe hyperfunction it was considered advisable, however, to discuss this whole group conjointly in the present chapter.

CLASSIFICATION

The various types of anterior-lobe hyperfunction can be subdivided according to the age of onset, the intensity of the manifestations, the underlying pathologic lesions, etc., but for practical purposes it suffices to subdivide this whole group as follows

(1) *Pituitary gigantism.*
(2) *Acromegaly.*
(3) *Cushing's disease.*
(4) *Mixed types* in which manifestations of several among the above-mentioned groups are simultaneously present.
(5) *Other types* of anterior-lobe hyperfunction, mainly characterized by a more or less selective increase in the production of thyrotrophic, gonadotrophic, diabetogenic, mammogenic, lactogenic, etc., hormones. These latter diseases are not yet sufficiently understood to warrant detailed discussion here.

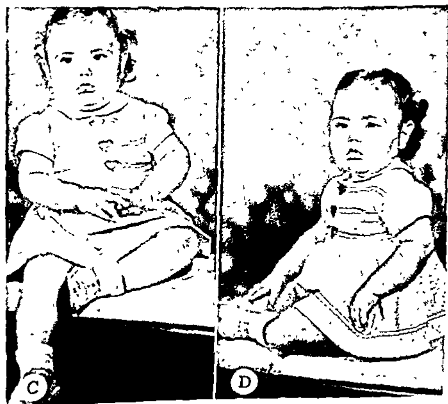
There are various types of GIGANTISM (e.g., familial, racial), but in the present chapter we shall only be concerned with that due to pituitary overfunction The latter results from an excessive production of somatotrophin in a young individual whose epiphyseal junction cartilages have not yet ossified, so that the bones are still capable of growth in length.

ACROMEGALY is a type of gigantism which usually occurs in an individual whose growth in length has become impossible since the junction cartilages have already ossified when the increased somatotrophin production of the pituitary commenced. It therefore results mainly in appositional bone growth in width or at the ends of extremities, and in proliferation of soft tissues.

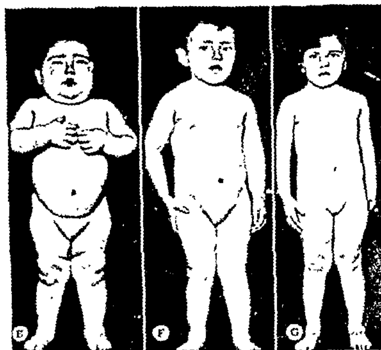


Acromegaly. — A. and B. 70-year-old Negro woman with a pituitary tumor Note prominent lips and nose characteristic of this race but exaggerated by the disease

(Courtesy of Dr J I Lobo)



(Cont'd on p. 297)





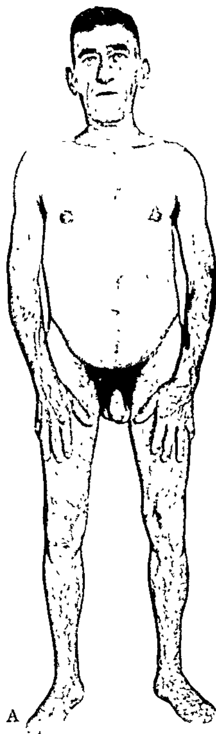
Development and recession of juvenile Cushing's syndrome. — A. and B. Age 1 year: appearance normal — C. and D. Age 16 months, beginning signs of adrenal-cortical hyperactivity — E. Age 18 months, extreme evidence of adrenal-cortical hyperactivity 17-KS 3.8 mg./24 hrs., one week prior to removal of left adrenal-cortical adenoma — F. Child 9 months postoperative, almost complete recession of the disease — G. 2 years postoperatively, appearance normal — H. Adrenal-cortical adenoma (140 gm.) removed; it contained hemorrhagic necroses and calcified deposits between neoplastic cortical cells.

(Courtesy of Drs. Robert W. Schneider and E. P. McCullagh.)



Clinical appearance suggestive of Cushing's syndrome (not verified by biopsy or autopsy). — A. and B. Woman age 36 years. Hirsutism, obesity (208 lbs.), blood pressure 218/140, diabetic tendency in glucose tolerance curve, B.M.R. +9%, Hb. 110%, RBC 5,400,000. Ruddy plethoric appearance of moon-shaped face. — C. Note plethora of face, obesity most marked on trunk, shoulders and neck.

(Courtesy of Drs. H. Lisser and C. K. Cangelo.)







Acromegaly. — A. 53-year-old man who began to develop acromegalic features 20 years ago, and insulin-resistant diabetes 10 years ago — B Note large nose, tongue and chin — C X-ray shows enlargement of sella, large para-nasal sinuses and widening of the angle of the jaw.
(Courtesy of Dr A B de Ulhôa Cintra)

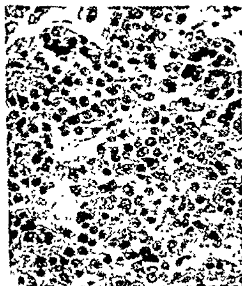
Sometimes we find mixed types of GIGANTISM WITH ACROMEGALY. Here the condition usually commences before the cessation of growth in length: this causes gigantism, but if increased somatotrophin production continues in later life, eventually acromegalic manifestations appear. Only rarely are there typical signs of acromegaly in children who are still capable of growth.

CUSHING'S DISEASE is a condition characterized by hypertension, glycosuria, osteoporosis, a peculiar type of facial and trunk obesity, purplish cutaneous striations and a florid complexion; in women there is hirsutism of the male type with amenorrhea and in men, impotence. The disease is due to basophilic or mixed-cell adenomas of the anterior-lobe and must not be confused with "Cushing's syndrome" in which the same clinical manifestations are due to adrenal tumors, lesions in the hypothalamus, thymus tumors or unknown causes.

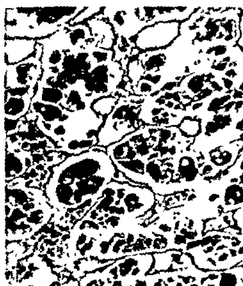
MIXED ANTERIOR-LOBE HYPERFUNCTION in which manifestations of acromegaly and Cushing's syndrome appear conjointly are not uncommon and this is one of the reasons why the various types of anterior-lobe hyperfunction are discussed here in the same chapter

PATHOLOGIC ANATOMY

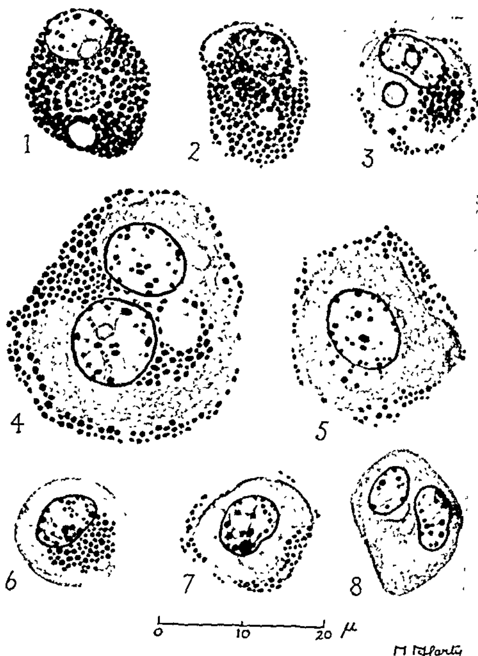
In PITUITARY GIGANTISM and ACROMEGALY the underlying lesion is an eosinophilic or mixed-cell adenoma (or carcinoma) of the anterior-lobe which may measure 1½ to 2 inches in diameter (see also "Tumors," p. 264) In CUSHING'S DISEASE — as originally described — the pathogenic agent is a basophil adenoma of the anterior-lobe, but this is a comparatively rare cause of the Cushing syndrome More frequently we find hyaline degeneration and vacuolization of the anterior-lobe basophils; in some cases the anterior-lobe shows no histologically-detectable abnormalities. It should be emphasized, however, that voluminous anterior-lobe tumors are rarely found in Cushing's disease; this accounts for the infrequency of radiologic signs of a hypophyseal neoplasm in patients suffering from this malady



Hypophysis in acromegaly. Note uniformity of structure in this adenoma which consists exclusively of eosinophils (High magnification) (Courtesy of Dr W Boyd)



Hyalinization of basophils in Cushing's syndrome Note large, darkly staining basophils, whose cytoplasm is homogeneous ("hyalinized") and contains irregular, light vacuoles Patient suffered from typical Cushing's syndrome



Hyaline changes in pituitary basophils frequently associated with Cushing's syndrome. (1) Normal mature basophil cells. Note eccentric nucleus and light circle corresponding to "negative Golgi image", the cytoplasm is filled with coarse basophil granules and there is one vacuole, but no homogeneous hyalin material. (2-8) basophil cells affected by increasing degrees of hyalinization. Some of the basophils are binucleated (4,8) and only in two of them (2,3) is the negative Golgi image detectable. Such lesions are not absolutely constant, but very characteristic of Cushing's syndrome. (After A. C. Crooke. J. of Path. and Bact. 41: 339. 1935)

INCIDENCE

Anterior-lobe hyperfunction is probably quite common but most pertinent cases manifest themselves as secondary hyperthyroidism, hypercorticoidism, hypergonadism or hypophyseal diabetes mellitus.

True PITUITARY GIGANTISM is comparatively rare and of course occurs only in young, growing individuals.

ACROMEGALY is likewise rare; it is estimated to occur about once per 15,000 hospital admissions. About half of all cases appear during the third decade of life, but the fully-developed clinical syndrome may not be manifest before the fifth decade.

True CUSHING'S DISEASE is one of the least common endocrine diseases.

PATHOGENESIS

The causative pituitary lesions have been discussed above (see : Path. Anat. p. 299). Suffice it to say here that hypophyseal GIGANTISM is due to the growth-promoting effect of somatotrophin which accelerates new bone formation, especially at the junction cartilages. At the same time, there is a fairly proportionate increase in the size of the various organs and soft tissues.

In ACROMEGALY the increased somatotrophin production can no longer stimulate growth in length, since the disease occurs after the union of the junction cartilages. Nevertheless, the growth of those bones which are independent of junction cartilages (periosteal bone formation) and that of the soft tissues (e.g., internal organs, skin) continues: this gives rise to the typical acromegalic appearance.

CUSHING'S DISEASE is generally ascribed to an increased corticotrophin secretion which in turn augments the secondary corticoid hormone production The fact that the adrenal cortices are often enlarged and that partial adrenalectomy tends to exert a curative effect is in accordance with this interpretation. Some investigators assumed, however, that at least the characteristic hyalinization of the basophil cells may be secondary rather than the cause of the disorder. In some instances, hypothalamic lesions appear to be the primary cause of the malady It is possible that derangements in the hypothalamic region may increase corticotrophin production in the same manner in which tumors of the pineal region can apparently increase gonadotrophin secretion and elicit precocious puberty.

CLINICAL COURSE

State. — In PITUITARY GIGANTISM there is generalized, symmetric overgrowth of the skeleton and soft tissues so that well-proportioned giant types result. These are usually physically strong, mentally alert, intelligent individuals whose libido and potentia are above normal Occasionally however, gigantism is associated with genital hypoplasia and sometimes it is complicated by diabetes mellitus or hyperthyroidism.

In ACROMEGALY there is overgrowth of the short and flat bones, enlargement of the viscera, degenerative changes in the muscles, and often complication with hyperthyroidism or diabetes mellitus. The overgrowth affects mainly the ends (acra) of the body, namely the nose, chin, hands and feet, even the soft tissues of the "acra" (e.g., nose, lips, tongue) are enlarged.

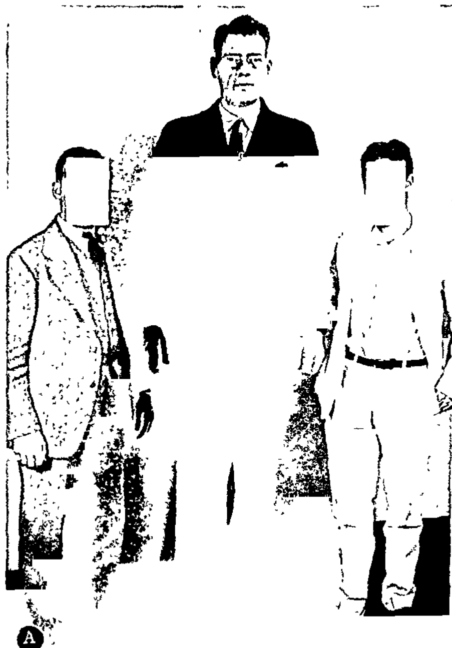
Both in pituitary gigantism and in acromegaly, enlargement of the sella, due to pituitary tumor, is comparatively common and frequently accompanied by signs of intracranial pressure

In CUSHING'S DISEASE the sella is rarely eroded, since large hypophyseal tumors are uncommon However, the following manifestations are characteristic, obesity of face, neck and trunk, hypertension, diabetes, osteoporosis, cutaneous striations and "virilization." Occasionally the patient complains of backache, abdominal pain, pains in the eyes, choking and suffocating sensations, convulsions and even fainting spells. Usually the general resistance, especially to infections is greatly decreased in Cushing's disease.

Metabolism. — The BODY TEMPERATURE and the B.M R. may be low, normal or high in the various types of anterior-lobe hyperfunction depending upon the functional activity of the pituitary An increase in the B.M R. is presumably the result of an excess

thyrotrophin production, while a decrease could result from a breakdown of pituitary tissue following compression or necrosis of hypophyseal tumors.

Disturbances in CARBOHYDRATE metabolism are characteristic both of acromegaly and of Cushing's disease, but are comparatively rare in gigantism. They can presumably be due to increased gluco-corticotrophin (and secondarily gluco-corticoid), diabetogenic principle and thyrotrophin production,



Acromegalic gigantism. — A. 27-year-old acromegalic giant (height approximately 7' 2½") The two normal men standing at either side are 5'9" and 5'10½" high respectively Note typical acromegalic facies, prognathism The fingers are so wide that a U S A 50 cent piece passes easily through his finger ring Voice extremely deep and hoarse, musculature relatively weak (Cont d on p 303)

since all of these hormones are conducive to hyperglycemia and even glycosuria.

Derangements in LIPID METABOLISM are especially noteworthy in Cushing's disease, which is characterized by a peculiar "buffalo type" of obesity, localized in the face ("moon face"), neck and trunk while the extremities remain comparatively thin. The blood lipid and blood cholesterol levels on the other hand show no constant deviation from the normal.

The anabolic effect of somatotrophin may result in marked NITROGEN retention in gigantism and acromegaly, but this is rarely the case in Cushing's disease. The N.P.N. rises only if secondary renal disease interferes with the excretion of the metabolic end-products of protein metabolism.

Disturbances in WATER AND SALT METABOLISM are likewise common in conjunction with the various types of anterior-pituitary hyperfunction. Polyuria is frequently observed, especially in acromegaly and Cushing's disease. It is sometimes due to accompanying nephrosclerosis and perhaps partly also to the diuretic effect of certain anterior-lobe hormones (e.g., thyrotrophin)

The blood PHOSPHATE level is often high (4-6 mg.%) in acromegaly, while Cushing's disease is sometimes conducive to the hypercorticoid type of electrolyte derangement, namely: a fall in blood potassium and chloride accompanied by alkalosis and a rise in blood sodium. These changes are presumably due to increased mineralo-corticotrophin production.

Growth and Bone Structure. — In PITUITARY GIGANTISM bone growth is excessive, but the skeleton remains proportionate. Many of these giants attain a size of 7 to 7½ ft., and in a few cases a height of 8 ft 9 to 10 inches has been claimed. Excessive growth may commence in early childhood, but usually it does not become evident before adolescence. If somatotrophin overproduction continues after ossification of the junction cartilages, acromegaly is superimposed upon the gigantism so that "acromegalic giants" result.

In ACROMEGALY usually one of the







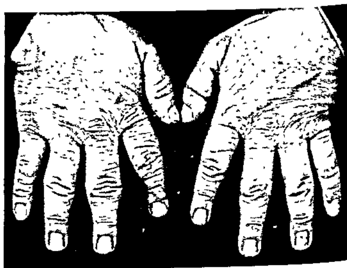
— B. Skull showing widening of the angle of the jaw and enlargement of sella and para-nasal sinuses. — C. X-ray of the greatly enlarged hand of the patient in comparison with a normal hand (Courtesy of Dr E P McCullagh)

first noticed signs is that the patient has to wear larger gloves and shoes than usual, because of the excessive growth of the hands and feet. The hands are not only large but especially broad ("spade hands") with thick, blunt "sausage fingers." The terminal phalanges may show "tufting." The supra-orbital ridges become very prominent and, if the disease develops comparatively early, the para-nasal (especially the frontal) sinuses are greatly enlarged. The growth of the mandible is especially pronounced. The angle of the jaw tends to straighten out while the chin turns upward; this often causes severe prognathism and a separation of the teeth, which "grow away from each other."



Acromegaly. Age 51 years, height 72½", weight 220 lbs Signs of acromegaly manifest during past ten years Note enlargement of lips, soft tissues of face and hands, exophoria (outward rotation of eye-ball) due to weakness of internal rectus muscle There is a large nodular goiter
to pres
are no

(Courtesy of Dr E P McCullagh)

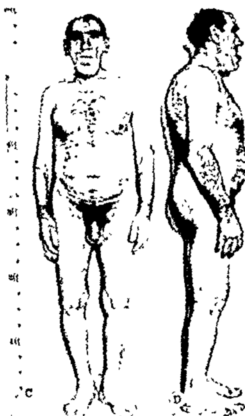


Hands in acromegaly. Typical acromegalic hands Note great increase in the development of the soft tissues

(Courtesy of Dr E J Kepler)







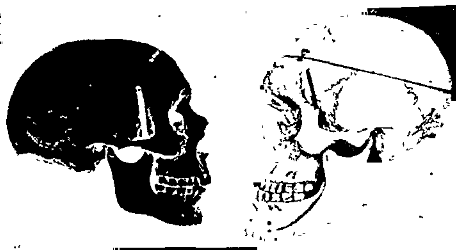


Acromegaly. — A. Note coarse features, enlargement of nose and lower jaw, deep naso-labial folds and heavy forehead wrinkling — B. Note prognathism and prominence of supraorbital ridge. — C. Note muscular build, hirsutism, large hands and feet and facial characteristics seen in Fig A — D. Note depth of chest, cervico-dorsal kyphosis, large hands and feet and facial characteristics seen in Fig B — E. Note enlargement of hands, particularly by the increase in width and sausage-like fingers (compared with normal male hand)

(Courtesy of Drs H Lisser and M N Goldberg)

Acromegaly. — A. Man, age 28 years, with manifest signs of acromegaly Note marked enlargement of sella, frontal and maxillary sinuses, marked opening of the jaw-angle with prognathism — B. Man, age 22 years, normal skull for comparison.

(Courtesy of Montreal Neurological Institute)

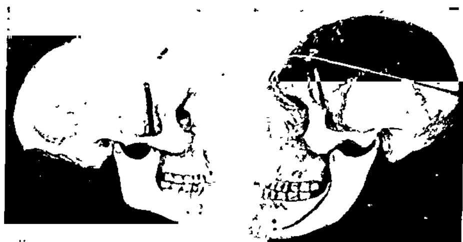


[illegible] Lateral aspect of a normal (left) and acromegalic cranium Note [illegible] andible, prognathism, and separation of the trans-sphenoidal operation

(After H Cushing and L M Davidoff Monographs of the Rockefeller Inst for Med Res No 22 1927)

Acromegaly. — A. Man, age 28 years, with manifest signs of acromegaly Note marked enlargement of sella, frontal and maxillary sinuses, marked opening of the jaw-angle with prognathism — B. Man, age 22 years, normal skull for comparison

(Courtesy of Montreal Neurological Institute)



Skull changes in acromegaly. Lateral aspect of a normal (left) and acromegalic cranium. Note prominent supraorbital ridges, opening of angle of mandible, prognathism, and separation of teeth The maxillary spur had been removed in the trans-sphenoidal operation

(After H Cushing and L M Davidoff Monographs of the Rockefeller Inst for Med Res No 22 1927)

Cushing's syndrome. Age 27 years Outstanding characteristics Obesity, chiefly of face and trunk, weakness, deep red 'moon-face'. Easy bruising, violaceus abdominal striae, arterial hypertension (216/148), gallop rhythm, headaches retinal hemorrhages and exudates, decalcification of spine and pelvis. — X-ray therapy to pituitary (1200 r.u. to each temple) was applied without obvious benefit Hence, about 4 months later, bilateral hemiadrenalectomy was performed — A, B and C. General appearance before therapy. — D. and E. 7 months following bilateral hemiadrenalectomy Complete symptomatic cure Arterial hypertension remains, blood pressure 188/138 Decalcification of spine slightly less. — F. Appearance of patient three years after adrenal surgery — G. X-ray five months preoperative Note more marked demineralization of the spine, and of the pelvis There appears to be a coincidental congenital deformity of the neural arch of the 5th lumbar vertebra. — H. Striking remineralization three years after operation The partially destroyed head of the right femur with secondary hypertrophic changes is presumably the result of an unrecognized fracture due to the disease

(Courtesy of Dr E. P McCullagh)







In addition to the above changes, X-ray of the skull usually reveals an enlarged sella often with erosion of the posterior clinoid processes; the calvarium — as the other flat bones — becomes greatly thickened

The bodies of the vertebræ increase in their antero-posterior dimensions, a



A



B



C

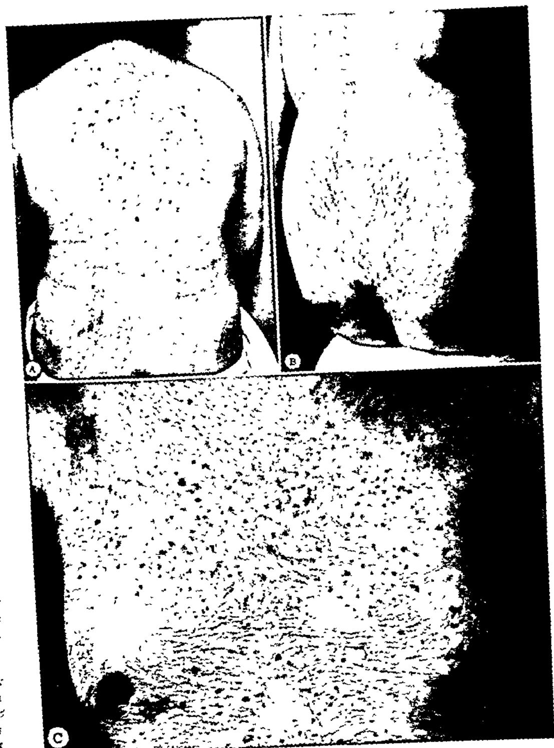


E



D

(Cont d on p. 309)



The skin in Cushing's syndrome. — A. Note the tendency of the skin to retain marks from clothing (due to skin edema?) — B. In this patient, hirsutism and keratosis pilaris are especially prominent. — C. Chest of a man with pituitary basophilism. Note prominence of acne, hirsutism and so-called "androgenic flush." The nipples are often pigmented even in the male, and the areolae large. (Courtesy of Dr. E. J. Kepler.)

fact which is especially obvious in lateral X-rays of the thoraco-lumbar spine. Exostoses often result from periosteal over-growth. The degenerative changes in the vertebræ may lead to *pronounced kyphosis.*

In CUSHING'S DISEASE osteoporosis, especially of the spine, is frequently pronounced and may lead to a kyphosis similar to that seen in acromegaly. The shoulders tend to become round, the stature may actually grow shorter as a result of the osteoporosis and the consequent collapse of vertebræ. However, excessive growth of the bones, in length and width, or enlargement of the sella is likewise rare.

Blood. — In pituitary gigantism and acromegaly the blood count is rarely abnormal, but in Cushing's disease there often is polycythemia and an increase in blood volume which are responsible for the characteristic florid complexion of these patients.

Cardiovascular System. — In pituitary GIGANTISM the cardiovascular system remains essentially normal in proportion with the large size of the individual. In ACROMEGALY and CUSHING'S DISEASE there tends to be a pronounced enlargement of the heart ("cor bovinum") and of the blood vessels; these changes are probably secondary to the rise in blood pressure Myocarditic scars are likewise frequent, especially in Cushing's disease. In this malady, apparently due to weakness of the peripheral vessels, there is also a great tendency to the formation of ecchymoses, even under *the influence of very slight* traumas.

Muscular System. — In pituitary gigantism the musculature is usually well-developed and physical strength is above average. In acromegaly and Cushing's disease on the other hand, the muscles show degenerative changes and there is great fatigability upon muscular exertion.

Nervous System and Sense Organs. — All kinds of pituitary tumors which increase intracranial pressure tend to cause HEADACHES, VISUAL DEFECTS, DIZZINESS and sometimes FAINTING SPELLS, irrespective of the type of their hormone production. Headache is estimated to occur in about 90% of all acromegalics but is much less common in Cushing's disease. The visual disturbances are sometimes due to choked discs but more frequently to encroachment of the tumor upon the optic chiasma with consequent bitemporal hemianopsia. The cause of this particular visual defect is that those fibers of the optic nerve tracts which supply the temporal part of the visual field are closest to the pituitary and hence first to be affected by an expanding tumor.

In gigantism and acromegaly an initial increase in LIBIDO, POTENCY AND GENERAL MENTAL CAPACITY is rather frequent. These individuals tend to be enterprising, energetic, ambitious persons until a final breakdown of the neoplastic tissue leads to secondary hypopituitarism with loss of libido and general apathy.

EXOPHTHALMOS is comparatively common in acromegaly, but rare with gigantism or Cushing's disease. It is frequently associated with an increase in the B.M.R. and presumably due to increased thyrotrophin production.

The extreme enlargement of the NOSE, TONGUE and LIPS so characteristic of acromegaly is not seen in typical gigantism or Cushing's disease.

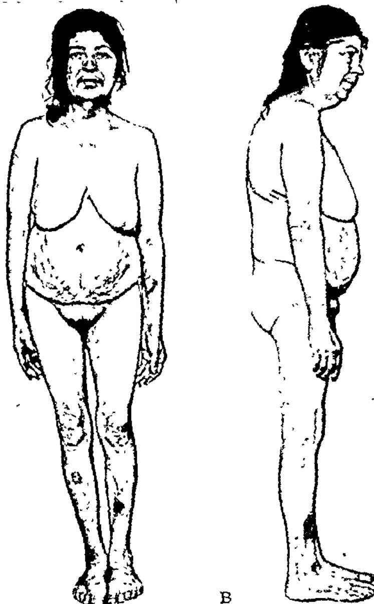
Respiratory System. — A tendency towards deepening of the VOICE, due to excessive enlargement of the larynx, is *noted in acromegaly but much* less common in Cushing's disease.

Digestive System. — All the visceral organs are greatly enlarged in the various types of anterior-lobe hyperfunction. In pituitary gigantism this enlargement remains proportionate to the rest of the body, while in acromegaly the viscera (heart, liver, pancreas, intestines, kidney, etc.) *are much greater* than would correspond to the body size. In Cushing's disease the heart and kidneys are often enlarged and the latter

taneous striations along the sides of the abdomen and thighs are especially characteristic of Cushing's disease.

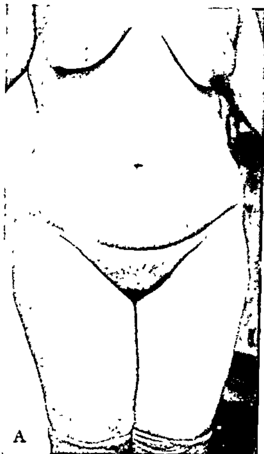
Urinary System. — The kidney is enlarged in pituitary GIGANTISM, but only *in proportion* to the body surface. In ACROMEGALY and CUSHING'S DISEASE the dimensions of the kidney are disproportionately large and microdissection studies have shown that the entire nephron is increased in length and width. In late stages of Cushing's disease (less frequently in acromegaly) there often is marked nephrosclerosis; this is partly responsible for the accompanying hypertension. *The* great predisposition of patients with Cushing's disease to various types of nephritis, especially ascending pyelonephritis, is likewise noteworthy.

Sex Organs — In early stages of pituitary GIGANTISM and ACROMEGALY the sex organs may be stimulated by pituitary gonadotrophins; but in the



Cushing's syndrome. — A. and B 38-year-old woman who developed some facial hair 2 years ago, amenorrhea 3 years ago and diabetes 18 years ago Clitoris of normal size, voice feminine, osteoporosis, typical abdominal striae, vascular fragility (note subcutaneous effusions on forearm and legs), emaciation, skin and muscle atrophy, hypertension (blood pressure 170/110), *insulin* resistance, blood cholesterol 132 mg%, CO_2-combining power, 64 vol %, blood Cl 80 m Eq/L, *blood* Na 134 m Eq/L

(Courtesy of Dr A B Ulhôa Cintra)





Cushing syndrome? — A. and B. 15-year-old girl with secondary amenorrhea, obesity and moderate hypertension Note abdominal striae but no excessive pigmentation of the areolae and no hirsutism (Courtesy of Dr J I Lobo)

may show signs of nephrosclerosis, but general splanchnomegaly is rare

Sclerosis or hydropic degeneration of the pancreatic islets is likewise noted in certain cases of acromegaly or Cushing's disease, especially in those accompanied by diabetes mellitus. These changes may well be due to excessive production of the so-called diabetogenic principle of the anterior-lobe.

Skin and Appendages. — In pituitary GIGANTISM the skin texture and hair distribution are essentially normal, while in ACROMEGALY there is pronounced increase in the thickness of the epidermis with hypertrophy of the skin papillæ and infiltration of the subcutaneous connective tissue. This causes great thickening and wrinkling of the skin, which is especially pronounced on the scalp, face and hands. It results in a coarsening of the features and adds to the characteristic enlargement of the hands, nose, lips and chin. In early stages there often is marked hirsutism and apical baldness, but later there may be complete loss of genital and axillary hair, due to breakdown of the tumor.

In CUSHING'S DISEASE the skin on the face becomes hyperemic with a reddish, sometimes bluish tinge which accounts for the florid appearance of these patients. There is hirsutism and shaving often becomes necessary in women. The body hair over the back, chest, arms, thighs and legs is likewise greatly increased and, due to some latent type of edema, the skin tends to retain the markings of tight clothing (e g, brassieres, corsets, belts). Ecchymoses and purpuric spots appear readily on slight trauma to the skin of the abdomen, thighs, arms, back. Acne, keratosis pilaris and purplish [illegible] cu-

Differential diagnosis of diseases due to anterior-lobe hyperfunction

Signs and Symptoms	Diabetes	Hyperthyroidism and Exophthalmus	Hypertension	Nephrosclerosis	Skeletal changes	Splanchnomegaly	Adiposity	Muscular strength	Sex organs	Skin	Age at onset	Visual disturbances	Other characteristics	Pituitary lesions
Pituitary Gigantism	N	N	N	N	Proportionate gigantism	N	N	N or +	First N or + later —	N	Growing children, rarely infants	+	Until late stages patient feels well	Eosinophilic or mixed adenoma sella large
Acromegaly	+	+	+	+	Large hands and feet, tufting of terminal phalanges, broad bones, osteoporosis of spine with kyphosis, thickened flat bones especially calvarium, large para-nasal sinuses, prognathism, prominent supra-orbital ridges, exostoses	+++	N	—	First + later —	Thickened with wrinkles, in late stages, often loss of pubic and axillary hair	Adults	++	Hyperphosphatemia	Eosinophilic or mixed adenoma, sella large
Cushing's Disease	+++	N	++	+++	Osteoporosis, especially of spine; collapse of vertebræ; kyphosis	++	"Buffalo" obesity	—	— (amenorrhea, impotence)	Striæ Hirsutism Acne Ecchymoses	Any age usually adults	N	Polycythemia Urinary calculi, high urinary 17-KS and corticoids	Basophilic adenoma, hyalinization of basophils or no change, sella small

\+ increase
— decrease
N no change (Normal)
In late stages of all three types of anterior-lobe hyperfunction, secondary break-down of the pituitary tumor may cause hypopituitarism

final stages, if the causative neoplasm begins to break down, atrophy of the testes, ovaries and accessory sex organs, loss of pubic and axillary hair, impotence in the male and amenorrhea in the female are the rule.

In CUSHING'S DISEASE amenorrhea, loss of libido and impotence are usually noted from the onset. Curiously, in spite of other signs of virilization (hirsutism, acne, etc.) the clitoral enlargement, so characteristic of the adrenogenital syndrome is absent.

COMPLICATIONS

Most of the common complications of anterior-lobe hyperfunction are those due to the causative pituitary tumor itself. Among these are visual disturbances, various neurologic manifestations due to invasion into, or compression of, the brain, hemorrhages into the tumor or liquefaction necrosis of the entire hypophysis with subsequent fatal hypopituitarism. All three types of anterior-lobe hyperfunction, but especially acromegaly and Cushing's disease, may be accompanied by marked, and often insulin-resistant diabetes mellitus or by hyperthyroidism.

Severe hypertensive disease with apoplexy and coronary complications are especially characteristic of Cushing's disease

Acromegaly and particularly Cushing's disease decrease the patients resistance to various types of stress and intercurrent infectious diseases are a frequent cause of death among them. This is presumably due to a derangement of the normal, adaptive pituitary-adrenal mechanism

DIAGNOSIS

Pituitary gigantism must be differentiated from simple PRIMORDIAL GIGANTISM. The latter is the counterpart of the so-called constitutional "primordial dwarfism" which has been discussed in the chapter on hypopituitarism. This is sometimes difficult since intermediate types between the two appear to be quite common. Even the constitutional form in which several members of a family, or race, are above average in size, apparently acts through genetic factors whose influence is mediated through the anterior-lobe and its somatotrophin production. Some investigators even speak of a "hyperpituitary constitution." It is generally agreed however, that primordial gigantism should be differentiated from pituitary gigantism on the basis of a demonstrable hypophyseal tumor in the latter cases.

Acromegaly is often confused with PAGET'S DISEASE, chronic PULMONARY OSTEO-ARTHROPATHY or LEONTIASIS OSSIUM, but the bone lesions characteristic of the latter conditions usually permit differential diagnosis. During PREGNANCY, changes suggestive of slight acromegaly are almost constantly demonstrable (thickening of the lips and nose, enlargement of the hands and feet, disturbances of vision, some splanchnomegaly) but the bony structures are usually not involved and after gestation the derangement disappears again.

This "forme fruste" of acromegaly has been ascribed to a temporary excess in anterior-lobe-hormone production during gestation.

CUSHING'S DISEASE may be difficult to differentiate from "Cushing's syndrome" (due to thymus neoplasms, adrenal tumors or hypothalamic injuries) especially since, unlike other types of anterior-lobe hyperfunction, Cushing's disease is rarely accompanied by manifest local signs of a tumor in the pituitary region. In doubtful cases it may be necessary to undertake surgical exploration of the adrenal and pelvic organs, the latter for possible accessory adrenals in the ovary or mesometrium, arrhenoblastomas and other virilizing neoplasms.

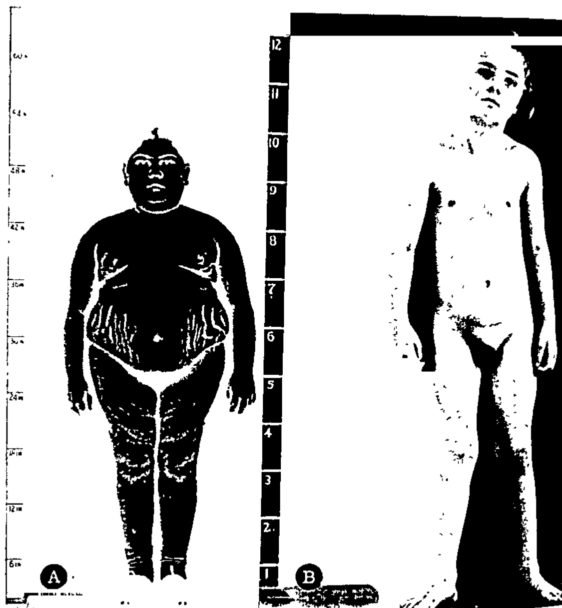
An increased elimination of corticoids and 17-KS is especially characteristic of Cushing's disease, but occasionally also tends to occur in acromegaly.

In the differential diagnosis of the three types of ant[illegible]

Differential diagnosis of diseases due to anterior-lobe hyperfunction

Signs and Symptoms	Diabetes	Hyperthyroidism and Exophthalmus	Hypertension	Nephrosclerosis	Skeletal changes	Splanchnomegaly	Adiposity	Muscular strength	Sex organs	Skin	Age at onset	Visual disturbances	Other characteristics	Pituitary lesions
Pituitary Gigantism	N	N	N	N	Proportionate gigantism	N	N	N or +	First *N or* + later —	N	Growing children, rarely infants	+	Until late stages patient feels well	Eosinophilic or mixed adenoma sella large
Acromegaly	+	+	+	+	Large hands and feet, tufting of terminal phalanges, broad bones, osteoporosis of spine with kyphosis, thickened flat bones especially calvarium, large para-nasal sinuses, prognathism, *prominent* supra-orbital ridges, exostoses	+++	N	—	First + later —	Thickened with wrinkles; in late stages, often loss of pubic and axillary hair	Adults	++	Hyperphosphatemia	Eosinophilic or mixed adenoma, sella large
Cushing's Disease	+++	N	++	+++	Osteoporosis, especially of spine; collapse of vertebræ; kyphosis	++	"Buffalo" obesity	—	— (amenorrhea, impotence)	*Striæ* Hirsutism Acne *Ecchymoses*	Any age, usually adults	N	Polycythemia Urinary calculi, high urinary 17-KS and corticoids	Basophilic adenoma, hyalinization of basophils or no change, sella small

\+ increase
— *decrease*
N no change (Normal)
In late stages of all three types of anterior-lobe hyperfunction, secondary break-down of the pituitary tumor may cause *hypopituitarism*



Comparison (
Patient at 11
and 6 months
in spite of her

(After Albright et al The Harvey Lectures Series 38 123 1942-43)

tion the summary chart on p. 315, may be of value.

PROGNOSIS

Both pituitary GIGANTISM and ACROMEGALY tend to "burn out" spontaneously; this is often due to liquefaction necrosis of the causative neoplasm Acromegaly very frequently runs a benign course lasting 30 to 50 years without ever resulting in secondary hypopituitarism. Only occasionally does the causative adenoma become malignant and result in death due to infiltration and compression of the brain. In most cases the fatal outcome is due to intercurrent infection and final cachexia, or some complication such as diabetic coma, hyperthyroidism, congestive heart failure, etc.

CUSHING'S DISEASE may likewise take a very chronic course with repeated spontaneous remissions. Death is fre-

quently due to complicating, hypertensive cardiovascular disease, renal complications or intercurrent infections.

THERAPY

In pituitary GIGANTISM and ACROMEGALY most physicians consider X-ray treatment of the pituitary region to be the therapy of choice. The eosinophilic cells are claimed to be more sensitive to X-ray than the chromophobes and hence irradiation is more frequently successful in gigantism and acromegaly than in the treatment of chromophobe adenomas. Because of technical difficulties, operation is usually contra-indicated, unless the tumor is very large and begins to encroach upon the optic tracts, thus threatening blindness.

In CUSHING'S DISEASE, X-ray therapy of the pituitary region has also been used with considerable success. Bilateral partial resection of hyperplastic adrenals or removal of complicating adrenal neoplasms is likewise often followed by temporary or even permanent remissions.

Treatment with folliculoids has been attempted in an effort to inhibit the hormone production of the hypophysis, but this is hardly justified in Cushing's disease, since folliculoids actually increase corticoid production (although they diminish somatotrophin secretion).

Several physicians recommend testosterone for the correction of the metabolic manifestations of Cushing's disease. In animal experiments, testoids tend to cause adrenal-cortical atrophy and to antagonize the nephrosclerosis-producing effect of anterior-pituitary extracts. The usefulness of this therapy in clinical medicine has not been fully verified, but it certainly causes symptomatic improvement.

POSTERIOR-LOBE HYPERFUNCTION

It has not yet been definitely established that excessive hormone production by the posterior-lobe can be the cause of a clinical syndrome. Nevertheless certain instances of DYSTOCIA, OLIGURIA, HYPERTENSION, DYSMENORRHEA, HYPERGLYCEMIA and even the syndrome of eclampsia have at times been regarded as due to excessive production of oxytocin and vasopressin respectively. The evidence in support of these theories is still unconvincing.

INTERMEDIATE TYPES OF HYPERPITUITARISM

As previously stated ACROMEGALY AND GIGANTISM may occur in combination, especially if hyperpituitarism commenced before, but continued after, ossification of the junction cartilages. Less frequently, symptoms characteristic of both ACROMEGALY AND CUSHING'S DISEASE manifest themselves in the same patient It is undoubtedly true therefore that overdosage with anterior-lobe hormones does not necessarily produce clear-cut types of the three main forms of anterior-lobe hyperfunction, since intermediate types are common Especially noteworthy among these are the forms in which otherwise typical acromegaly or Cushing's disease is associated with hyperthyroidism, hypergonadism, gynecomastia, persistent lactation, or diabetes mellitus, presumably due to excess production of thyrotrophin, gonadotrophins, "mammogenic principle," prolactin, or "diabetogenic principle" respectively.

The existence of a real "PANHYPERPITUITARISM" in which all parts of the pituitary would simultaneously become hyperfunctional has never been demonstrated, but it is not uncommon to observe hyperfunction of the anterior-lobe in combination with deficiency in posterior-lobe-hormone secretion. Thus, there may be acromegaly in combination with diabetes insipidus due to hyperfunction of an anterior-lobe tumor which compresses the posterior-lobe, and hence disturbs its function.

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has occurred in the field of steroid hormones during the following quarter of a century.

Within a short time *Doisy et al.* (1924) in the United States, and *Laqueur et al.* (1925) in Holland, not only demonstrated folliculoid activity in the fluid of Graafian follicles, but were able to prepare highly active concentrates of it.

The high concentration of folliculoid activity in human PREGNANCY URINE was discovered by *Aschheim and Zondek* (1927) in Germany. Subsequently *Haeussler* (1934) reported the surprising fact that STALLION'S URINE contains about 400 times as much folliculoid activity as that of women and *Zondek* (1935) found that stallion's testes are richer in folliculoid activity than any other tissue, containing about 500 times as much as human ovaries. Thus we learned that ovarian hormones are present in a variety of tissues and are by no means limited to the female sex.

Crystalline ESTRONE was first prepared in the United States by *Doisy et al.* (1929) (who described it under the name of "theelin,") and shortly afterwards in Germany by *Butenandt* (1929). ESTRIOL was isolated from the urine of pregnant women by *Marrian* (1930) in England, and was originally referred to as "trihydroxyestrin" or "estrone hydrate."

From human placenta, *Collip* (1930) prepared a crude extract having folliculoid activity; he gave it the name "emmenin" in the belief that it represented a new hormone. *Brown* (1932) isolated a crystalline compound from human placenta, which at that time was believed to differ from estriol in being comparatively less active in spayed rats This material was vaguely identified with "emmenin." *Butenandt and Browne* (1933) showed, however, that these crystals were pure estriol and that the originally observed differences in biologic potency were due to contamination with estrone of the early estriol specimens which had been used for comparison Subsequently *Marrian* isolated estriol-sodium-glucuronidate from placenta and it is now generally assumed that the folliculoid activity present in the original crude "emmenin" extracts was due to this substance.

ESTRADIOL, previously known as "dihydroxyestrin" was first obtained by reducing the ketone group of estrone (*Schwenk and Hildebrandt*, 1933). It probably represents the physiologic ovarian folliculoid as it is produced by the gonad and is the most active among the naturally-occurring substances of this kind.

From the urine of pregnant mares, several folliculoids were extracted by *Girard et al.* (1932-36) in France. They all proved to be chemically and physiologically very closely related to the previously known compounds of this type. In order to emphasize their equine origin, they were designated EQUILIN, EQUILENIN and HIPPULIN respectively.

Dodds et al. (1938) in England discovered that "stilbestrol," a stilbene derivative, possesses pronounced folliculoid properties and is highly active by mouth. This opened a new field by showing that compounds other than steroids may exert actions similar to those of steroid hormones.

Luteoids. — *Prenant* (1898) in France was the first to call attention to the GLANDULAR APPEARANCE OF THE CORPUS LUTEUM CELLS, a fact which led him to believe that this organ was an endocrine gland. In Germany, *Ludwig Frænkel* (1902) a few years later, showed that in the rabbit, NIDATION OF THE OVUM cannot occur if the corpora lutea are destroyed. This observation gave support to the endocrine theory of the corpus luteum cells. *Bouin*, the well-known histologist of Strasbourg (France) showed, a few years later (1906) that whenever a corpus luteum develops, the endometrium of the rab-

IV

THE OVARY

●

HISTORIC INTRODUCTION

Morphology. — The existence of the ovary, "the female testis" as it was called, has been known to ancient physicians since time immemorial, but ovary and testis were considered to be identical in structure. In 1673, the Dutch physician *Regnerus de Graaf* described small fluid-filled blisters which are visible on the ovarian surface during the fertile period of life. These "Graafian Follicles" were the first of the morphologic details observed in the ovary, merely because they are macroscopically visible Subsequently, in 1827 the Russian anatomist *von Baer* saw the human ovum. In view of its large size, this structure is on the borderline of naked eye visibility, hence it could be detected with comparative ease, using the primitive microscopes of that era.

Removal and Transplantation of the Ovaries. — The first ovariectomies in women were performed by *H. Hauston* (1701), *MacDowell* (1809) and the famous Georgia surgeon *Robert Battey* (1872) who were severely criticized by their contemporaries for undertaking such a dangerous task These operations were done to remove ovarian tumors, without realizing that the gland exerts an endocrine function.

In 1896, *Knauer* proved that ovarian TRANSPLANTS may re-awaken the extinguished sexual cycle of spayed animals and concluded that apart from the production of ova, the female gonads exert an important function in regulating estrus phenomena.

Folliculoids. — Subsequently, *Marshall and Jolly* (1906) and *Adler* (1911) demonstrated the artificial production of estrus in spayed animals receiving aqueous OVARIAN EXTRACTS Most of these early observations were not very clear-cut however, since ovaries store remarkably little hormone and hence the latter is difficult to demonstrate without using methods of purification and concentration.

In 1912, *Fellner* reported the surprising fact that PLACENTAL EXTRACTS have an effect upon ovariectomized rabbits similar to that of ovarian extracts, probably because the placenta contains ovarian hormones.

Work along these lines was seriously handicapped however by the absence of a convenient BIOASSAY METHOD for the estimation of folliculoid compounds Prior to 1923, most investigators used the uterus of immature or spayed animals as an indicator of folliculoid activity and hence they had to kill the animals for each test. It was of great importance therefore, when, based on previous observations (*Stockard and Papanicolaou*, 1917; *Long and Evans*, 1920) of regular cyclic variations in the vaginal epithelium of rodents, *Allen and Doisy* (1923) described their well-known test for folliculoid substances. This technic is based on the cornification of the vaginal epithelium of spayed rats and mice produced by treatment with folliculoid compounds. It may be safely said that this simple and accurate test has been the basis for all further work on the purification of folliculoids and acted as one of the greatest stimuli for the rapid development which

from human pregnancy urine. Subsequently, in 1938, these same investigators demonstrated that injected progesterone is eliminated in the urine as pregnanediol sodium glucuronidate indicating that at least in man, this compound is an important end-product in the metabolism of progesterone. This observation opened the way for the many interesting studies concerning the metabolism of progesterone which were performed using pregnanediol elimination as an indicator.

Gonadotrophins. — The fact that the ovary is dependent upon certain trophic stimuli had been foreseen as early as 1914 by the Danish investigator, *Knud Sand*, who spoke of "X-SUBSTANCES" as indispensable for gonadal development and function. *A. Lipschutz* (1925) found that ovarian grafts grow better in spayed than in intact animals, hence he also concluded that extragonadal trophic influences are important regulators of ovarian growth. As previously stated in the chapter concerned with the history of pituitary research, this conception received ample confirmation later through the demonstration of the pituitary gonadotrophic hormones.

Ovarian Diseases. — Female HYPOGONADISM as well as various types of MENSTRUAL ANOMALIES, were known to the physicians and laymen of antiquity

Parallel with the previously mentioned experimental observations, it gradually became clear that the folliculoids secreted by the ovarian follicle are responsible for estrus in animals and postmenstrual changes in women, while the luteoids, coming from the corpus luteum, cause progestational transformation of the endometrium and prepare the uterus for the nidation of an ovum. Menstruation was recognized as due to sudden withdrawal of these ovarian hormones at the end of the sexual cycle (*Frankel*, 1910; *R. Meyer*, 1913; *Schroder*, 1913; *Novak*, 1921; etc.).

A great deal can be learned from the spontaneous experiments which nature performs when one or the other ovarian structure is hypofunctional or selectively proliferates in an exaggerated manner. In the ovary, true neoplasms are not always readily distinguishable from other types of abnormal growths. They will be discussed here conjointly, grouped according to the type of clinical syndrome they provoke. In this manner we shall see how the ovarian diseases helped us to recognize the cell types which are responsible for the production of the different hormonal principles.

Complete primary APLASIA or AGENESIS of the ovaries was repeatedly reported in the early literature, but it was not until recently that *Turner* (1938) and *Albright et al.* (1942) clearly recognized that the clinical syndrome associated with this malformation is characterized by short stature, inhibition of sexual development, high urinary gonadotrophin titers and congenital anomalies, such as coarctation of the aorta, webbing of the neck, etc

AMBISEXUALITY has raised a great deal of interest, ever since the earliest periods of recorded history. Hermaphroditos, the ambisexual "son" of Aphrodite and Hermes, was a beautiful, sacred and rather romantic figure in early Greek mythology. Some of the most distinguished Hebrew writers interpret the first chapter of Genesis as describing Adam as being of both sexes Be this as it may, *Theophrastos* (372-287 B.C) in his "Characters" describes ambisexual human beings to whom the name "hermaphrodite" is now assigned.

Most of the ambisexual people are PSEUDOHERMAPHRODITIC, that is, they only possess the gonads of one sex, but have both male and female accessory sex characteristics. Probably the first

bit undergoes a PROGESTATIONAL TRANSFORMATION assuming the appearance of lace ("dentelle utérine"). Later, in Germany, *Fellner* (1913) and *Herrmann* (1915) were able to produce this same characteristic lace-like endometrium with corpus luteum extracts. A few years earlier in the United States, *Loeb* (1908) had discovered the importance of the corpus luteum in the formation of DECIDUOMAS in guinea-pigs. These are tumor-like structures resembling the maternal placenta, which occur following local trauma in the endometrium but only if corpora lutea are present in the ovary. All these observations helped to support the view that the corpus luteum is a distinct gland of internal secretion.

The important rôle played by the corpus luteum in the MAINTENANCE OF PREGNANCY was demonstrated by *Corner* (1928) who succeeded in maintaining gestation in the spayed rabbit by means of a corpus luteum extract.

Progress along these lines was very slow however, until 1929 when two American anatomists *Corner and Allen* described a simple bioassay technic based upon the ability of luteoids to cause progestational transformation in the rabbit

Using this test and modifications of it, the work of chemists advanced rapidly. CRYSTALLINE CORPUS LUTEUM HORMONE preparations have been described in the United States by *Hisaw et al.* (1930); *Fevold et al.* (1932) and *Allen* (1932) and in Germany by *Fels and Slotta* (1931), but none of these authors gave an adequate description of the physical and chemical characteristics of their crystals. The ketonic properties of the hormone were first recognized by *Butenandt* (1934) and *Hartmann and Wettstein* (1933) The first pure PROGESTERONE crystals were prepared by *Butenandt* (1934) in Germany, and independently, by *Wintersteiner and Allen* (1934) in the United States. Almost at the same time, *Slotta et al.* (1934) were able to establish the now generally accepted formula of progesterone. The partial SYNTHESIS OF PROGESTERONE (from stigmasterol) has been accomplished by *Butenandt et al.* and *Fernholz* (1934).

The most interesting aspect of this historic survey is the great part played by the above-mentioned two bioassay methods for folliculoid and luteoid activity respectively. These were described within the same decade and made possible an extraordinarily fruitful period of work by chemists who within a few years, isolated and clarified the structure of the most important ovarian hormones. This is all the more noteworthy since before the description of the above tests practically no progress had been made along these lines, in spite of centuries of persistent and industrious work.

It must be realized that a test object for a hormonal activity is of little use unless it is accurate and simple. Tests for ovarian hormone activity were known much before 1923, but since they were too cumbersome and inaccurate, they served merely to demonstrate the possibility of preparing active ovarian extracts The above-mentioned superior technics had to be developed before chemists could readily check the biologic value of their preparations whenever a new fraction or compound was obtained. This simplicity of assay was instrumental in interesting chemists of distinction to pursue these problems

PREGNANEDIOL was first prepared from human pregnancy urine by *Marrian* (1929) in England. *Venning and Browne* (1937) in Canada, found that the compound is actually eliminated as pregnanediol sodium glucuronidate — that is, a sodium salt of the glucuronide — since it is in this form that they were able to isolate this steroid

are not alveolar sarcomas, but represent a distinct type resembling certain ovarian neoplasms, which were subsequently described by *Masson* (1912) as "seminomas of the ovary." *Strong* (1919) spoke of them as "embryonal carcinomas"; the term "dysgerminoma" was proposed by *Meyer* (1930) because he claimed that the tumors arise from the germinal epithelium which loses its "germinal" properties as a result of some derangement occurring before its differentiation into ovarian or testicular tissue. The recent discovery of true seminomas of the testis, which proved to be essentially different from all ovarian tumors, clearly shows that the "dysgerminoma" is a false seminoma. (See : False seminomas.)

The STRUMA OVARII was usually misinterpreted by pathologists who found it very difficult to understand that true thyroid tissue could occur within the ovary. Thus tumors now known to belong to this group were diagnosed as "folliculoma malignum," a type of "endothelioma," or ovarian metastases of undetectable primary thyroid growth.

Thyroid tissue in the ovary had been described by several early investigators, but it was *Pick* (1920) who recognized that these growths are actually teratoids in which the thyroid tissue predominates to such an extent that all other constituents are "crowded out" by it. This interpretation is further supported by the many intermediate types between ordinary embryomas with small nodules of thyroid tissue and tumors consisting exclusively of the latter.

The CHORIONEPITHELIOMA of the ovary was originally described in 1900 by *Kaufmann* but it was only as a result of considerable additional work that it was definitely recognized as a placental neoplasm

Probably many cases of "vicarious menstruation" — known to physicians and laymen since the early ages — are the result of bleeding from an ectopic endometrium. The same is true of the "tarry" or "chocolate cysts" in the ovary and the pelvic peritoneum, frequently described early in the nineteenth century. v *Rokitansky* (1860) was probably the earliest investigator to recognize internal ENDOMETRIOSIS as an independent form of disease. *Russell* (1899) was the first, however, to describe endometrial tissue in the ovary *Sampson's* (1921) classic investigations convinced most workers that at least in some cases, if not in all, ectopic endometrium grows in the pelvis because it has been regurgitated there through the oviducts at the time of menstruation.

NORMAL MORPHOLOGY

ANATOMY

In man, the ovaries are paired, almond-shaped bodies situated on either side of the uterus, near the lateral wall of the pelvis. They are attached to the back of the broad ligament, behind and somewhat caudad from the uterine tubes. Their color is greyish-pink and their surface smooth or, especially in older women, puckered by numerous small scars During the fertile period of life, small fluid-filled blisters are distinguishable on the ovarian surface; these are the follicles of de Graaf

The two ovaries are approximately of equal size, measuring about 4 cm. in length, 2 cm in width and 8 mm. in thickness They weigh 2.0-3.5 gm each. In its natural location, the ovary is so oriented that its upper pole is near the free end of the Fallopian tube, the lower pole or uterine extremity is connected with the origin of the tube from the uterus. The tubal pole lies near the external iliac vein, attached to the ova-

instance of a TRUE HERMAPHRODITE, that is to say, a person having both testicular and ovarian tissue, was described by *Klotz* in 1879.

It is interesting to note that in view of recent observations, the whole conception of ambisexuality as an essentially abnormal process has to be revised. We know now that "female" sex hormones, such as folliculoids, are produced by the testis as well as by the ovary and that even certain hormones themselves (e g., ethynyl-testosterone) are ambisexual since they stimulate both male and female accessory sex characteristics. It becomes increasingly more evident that a certain degree of ambisexuality is normal and that only the extremes of this condition are pathologic.

TUMORS OF THE OVARY have interested physicians since time immemorial, because of the enormous size which they may attain and because of their great morphologic and functional diversity. Here we shall mainly consider the history of those tumors, and related abnormal growths, which cause or are caused by endocrine disturbances.

The SIMPLE FOLLICLE CYST was first differentiated from other ovarian cysts by *Rudolph Virchow* (1848). It was not *until the beginning of the 20th* Century, however, that this distinction was supported by functional evidence of a resulting HYPERFOLLICULOIDISM, especially metropathia hemorrhagica (*Robert Meyer, Schroder*).

v. Rokitansky (1855) is usually credited with having described the earliest typical case of OVARIAN SMALL-CYSTIC DEGENERATION; however, his patient suffered from a hydatidiform mole and the ovarian lesion was only secondary. The first characteristic cases, associated with menstrual disturbances and other signs of hyperfolliculoidism, were reported towards the end of the 19th Century (*Bulius; Petit*, etc.).

A typical OVARIAN FOLLICULOMA was apparently described by *v. Rokitansky* in 1859 although he did not specifically classify the tumor *v. Kahlden* (1895) deserves credit for first distinguishing as a separate entity, an "adenoma of the Graafian follicle," containing folliculoid and cylindromatous areas which produced hyperfolliculoidism

METROPATHIA HEMORRHAGICA was described by *Olshausen* (1875) under the name of "endometritis fungosa." It was subsequently shown by *Schröder* (1915) that this is not an inflammatory disease. He gave it the now generally accepted name "metropathia hemorrhagica."

Hewitt (1857) was the first to describe "Ovaries showing false corpora lutea with commencing cystic disease," but it was only much later (*Halban*, 1915; *Fraenkel*, 1922) that the corresponding pregnancy-like clinical syndrome was ascribed to the PERSISTENT CYSTIC CORPORA LUTEA.

v. Rokitansky (1859) was probably the first to describe a LIPID CELL TUMOR in the ovary. Later *Peham* (1899) attempted a detailed analysis of such a case both clinically and morphologically. He emphasized the resemblance of the growth to the zona glomerulosa of the adrenal cortex and called attention to the high glycogen content of its cells.

TUBULAR ADENOMAS of the ovary, frequently associated with virilism, have been known for a long time. *Dick* (1905) described them under the name of "adenoma tubulare, testiculare ovarii," *Robert Meyer* (1914-30) first referred to them as "adenoma tubulare ovarii," subsequently as "andreioblastomas," and still later, as "arrhenoblastomas" He deserves credit for having clarified many points in connection with their morphology and pathogenesis.

The "SEMINOMAS" of the testis were first described by *Chevassu* (1906). He recognized that, contrary to the opinion of earlier workers, these tumors

are not alveolar sarcomas, but represent a distinct type resembling certain ovarian neoplasms, which were subsequently described by *Masson* (1912) as "seminomas of the ovary." *Strong* (1919) spoke of them as "embryonal carcinomas"; the term "dysgerminoma" was proposed by *Meyer* (1930) because he claimed that the tumors arise from the germinal epithelium which loses its "germinal" properties as a result of some derangement occurring before its differentiation into ovarian or testicular tissue. The recent discovery of true seminomas of the testis, which proved to be essentially different from all ovarian tumors, clearly shows that the "dysgerminoma" is a false seminoma. (See : False seminomas.)

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rian fimbria of the oviduct and a fold of peritoneum, the SUSPENSORY LIGAMENT of the ovary. The uterine pole is connected with the uterus near the origin of the oviduct by a rounded solid cord, the OVARIAN LIGAMENT. The latter is enclosed within the broad ligament and contains smooth muscle fibers. Between the two poles is the mesovarian border of the ovary, which is attached to the dorsal lamina of the broad ligament by a short fold, the MESOVARIUM. It is through this fold that the ovarian nerves, vessels and lymphatics pass.

The organ is enclosed in the OVARIAN FOSSA on the lateral wall of the pelvis. This pocket is delimited by the external iliac vessels above, the obliterated umbilical artery in front and the ureter behind.

Near the ovary are two vestigial structures :

(1) The EPOOPHORON (organ of Rosenmuller; parovarium) which lies in the mesosalpinx between the ovary and the oviduct. It consists merely of a few short tubules which converge towards the ovary, while their opposite ends open into a rudimentary longitudinal duct (duct of Gartner).

(2) The PAROOPHORON, which consists of irregular rudimentary tubules in the broad ligament between epoophoron and uterus Usually these tubules are well-developed only in children.

HISTOLOGY

The ovary consists of a peripheral CORTEX which contains the various stages of maturing follicles, corpora lutea and their scars, and of a MEDULLA consisting of connective tissue stroma, blood vessels, lymphatics and nerves

The Germinal Epithelium. — This is a simple or stratified lining of cuboidal or columnar cells separated from the underlying ovarian tissue by a basement membrane. Between these undifferentiated cells are found at irregular intervals large round cells, the primordial sex cells. In the embryo, and perhaps to some very slight extent even during early postnatal life, this epithelium gives rise to ova which invade the underlying tissue. In adults it becomes gradually flattened and increasingly similar to the ordinary peritoneal mesothelium. Strictly speaking, the ovary possesses no capsule although the egg-free surface layer of dense stroma is often described as such under the name of TUNICA ALBUGINEA.

The Follicles.— Scattered throughout the ovarian cortex are about 500,000 FOLLICLES in various stages of maturation. Ordinarily only one of these reaches full maturity during each menstrual cycle and most of them undergo degeneration without ever having fully developed. Hence in the adult, the number of follicles gradually decreases and in senile women, very few, if any, persist.

The most immature stage in the process of maturation is represented by the PRIMARY FOLLICLES. The vast majority of the ova in the normal adult ovary are stored in such immature follicles only a few maturing at any one time. The primary follicles, most numerous in the periphery of the gonad, are roundish bodies of about 45μ in diameter They consist of a centrally-located large, roundish, egg cell or ovum surrounded by a single layer of flat or cuboidal so-called *follicular or granulosa cells*. The latter are so poor in cytoplasm that early histologists described them merely as granules; hence the term "granulosa layer."

The GROWING FOLLICLES enlarge chiefly through the proliferation of the follicular cells. The originally single granulosa-layer becomes stratified, while the ovum reaches a diameter of 60-80μ and surrounds itself with a thick cell-membrane, the *zona pellucida*, so called because of its semi-transparent aspect.

In the granulosa, certain cells degenerate and droplets of fluid accumulate around them. The deeply basophilic, degenerating granulosa cells are referred to as *Call-Exner* bodies, while the fluid droplets represent the first stages in the secretion of the so-called *follicular fluid* or *liquor-folliculi*. Due to the confluence of several of these droplets and the ever increasing amount of liquor folliculi, a cyst-like cavity, the *antrum folliculi*, is formed between the granulosa cells when the follicle reaches a diameter of about 0.2 mm. The fluid pushes the ovum with some surrounding granulosa cells to one side, so that the egg is enclosed in a small hillock, the *cumulus oöphorus* or *discus proligerus*, which protrudes into the follicular fluid.

During this growth, the connective tissue surrounding the granulosa cells differentiates into a capsule, the *theca folliculi*, separated from the granulosa by a homogeneous *basement membrane*. Within the theca, we distinguish · (1) an internal layer (theca interna) immediately surrounding the basement membrane and containing many capillary vessels, and (2) an outer layer (theca externa) consisting of spindle-shaped, concentrically arranged cells and connective tissue fibers In many animal species the theca does not differentiate into these two layers and even in man the borderline, between the external and internal layers, is indistinct.

The further maturation of the follicles is chiefly due to the accumulation of increasing amounts of follicular fluid. The MATURE OR GRAAFIAN FOLLICLES measure about 10 mm. in diameter and are fluid-filled cysts, lined by a thin layer of *granulosa cells*; within this lining is the cumulus oophorus with the ovum At this stage, the follicles reach the ovarian surface and bulge outward into the peritoneal cavity preparatory to rupture The immature follicles tend to migrate towards the surface in the course of their maturation, partly owing to their increasing size and partly by actual outward movement, perhaps due to traction by some of the theca cells. On that pole of the follicle which lies closest to the ovarian surface, a few theca cells, the *"theca interna cone"* of Strassman, develop a definite tropism for the ovarian surface and actually infiltrate through the stroma in the direction of the tunica albuginea It is assumed that the granulosa secondarily protrudes into the loose connective tissue of this cone, thus gradually reaching the surface.

In the fully-developed mature follicle, the *granulosa cells* have a diameter of about 10μ. They contain but little cytoplasm and a nucleus with 1-3 nucleoli. At any time many granulosa cells are found in the process of mitosis The follicular cells of the cumulus oophorus region assume a columnar, elongated and polyhedral shape, their longitudinal axes taking a radial position from the center of the ovum. This region consisting of 12-20 layers of granulosa cells is called the *corona radiata*. It is attached to the zona pellucida by radial fibrils. The *ovum* of the mature follicle has a diameter of 120μ; it is the largest cell in the human body. Its eccentrically-located nucleus measures 25μ in diameter and has a thick membrane and a large nucleolus, the "macula germinativa." Its cytoplasm contains some yolk granules, but the mammalian ovum is much poorer in yolk than that of oviparous animals (e.g., birds)

Eventually the superficial, bulging membrane of the mature follicle becomes extremely thin and *ovulation* occurs upon its rupture. At this time the follicular fluid and the ovum, together with the surrounding corona radiata and discus proligerus, are ejected into the peritoneal cavity or into the contiguous ostium of the oviduct. It is believed that the granulosa cells of the cumulus oophorus furnish nourish-

ment to the young ovum until implantation. In some animals, ovulation occurs only after mating; in others, including man, it takes place at regular intervals. (See . Estrus and Menstruation.)

Preparatory to fertilization, the ova have to undergo a process of MATURATION. In the adult mammalian ovary, the ova are primary ovocytes, corresponding to the primary spermatocytes of the male. After completion of their growth, these undergo two successive maturation divisions, the resulting four cells having only half the number of chromosomes of the original primary ovocytes (haploid number).

The *first maturation division* takes place immediately before or after ovulation and divides the nuclear chromatin evenly, but one of the daughter cells receives practically the entire cytoplasm and forms the secondary ovocyte (corresponding to the secondary spermatocyte in the male), the other is a minute granule, the *first polar body*, which subsequently divides again and eventually degenerates. Immediately after elimination of the first polar body, the secondary ovocyte undergoes a *second maturation division*, the spindle of which remains in the metaphase until fertilization is completed The chromatin is again equally divided, but (each daughter cell contains only half the number of chromosomes present in the mother cell) the cytoplasm remains with one daughter cell, that which forms the ovum (corresponding to the spermatid of the male); the other minute abortive cell is the *second polar body*. As a general rule the halving of the chromosomes, or "miosis," occurs during the first maturation division, although in some animals it takes place only when the second polar body is formed.

The number of chromosomes varies in the different species, but two of them are slightly different from the rest in their shape; these determine sex In man, there are forty-six somatic and two sex chromosomes. In the human ovum, both sex-chromosomes are similar (X-chromosomes), while in the spermia, they are different, only one resembling the female type (X and Y-chromosomes). At the time of fertilization, the final mature gonocyte contains only one of the sex-chromosomes, after the haploid division. In ova, this is necessarily an X-chromosome, while in spermia, it can be either X or Y. It is evident that following the union of the male and female gonocytes, the resulting cell will either have the X + X or the X + Y constitution, depending upon which paternal sex-chromosome was added to the maternal chromosome. Hence, the father can only blame himself for his offspring's sex.

Comparatively little is known about the *migration of the ovum* from the ovary into the uterus. It is assumed that unfertilized human ova remain viable only for about 24 hours after ovulation, so that migration into the tube, where fertilization normally occurs, must be rapid. Opinions differ concerning the relative rôle played by the musculature and the epithelial cilia of the tube in promoting the downward migration of the ovum.

FOLLICULAR ATRESIA is a degenerative phenomenon which affects a great many follicles before they mature sufficiently to produce a fertile ovum. It is estimated that in a normal human ovary there are about 20,000 atretic follicles at any time. It has been pointed out that even in a woman whose reproductive life lasts 35 years and who discharges an ovum every month throughout this period, only 420 follicles can mature to the point of ovulation. Since, on the other hand, all of the approximately 500,000 ova of infancy disappear during the course of life, it is obvious that the vast majority of the follicles degenerate before reaching maturity

Follicular atresia commences with the degeneration of the granulosa cells and

the ovum. Their place can be occupied by invading connective tissue (*obliterative atresia*), so that a hyaline scar-like tissue is formed; or by liquid so that a cyst results (*cystic atresia*). The former type more frequently affects the small, the latter the large follicles. *Sometimes parthenogenetic* egg-divisions accompany the phenomenon of atresia. The basement membrane between theca and granulosa becomes thick and assumes a hyaline, glass-like aspect during atresia. This so-called "*glassy membrane*," tends to persist much longer than other constituents of the follicle. Some histologists like to reserve the term "*corpus nigricans*" for the blood-pigment-containing, and "*corpus albicans*" for the pigment-free, corpus luteum scars; the atretic follicle being designated as "*corpus candicans*." In common usage the adjectives candicans and albicans (both of which mean white) are employed interchangeably for the pigment-free scars of either corpora lutea or follicles. This is especially justified in the case of old scars in which degenerated ova are no longer visible so that it is not possible to differentiate between follicle and corpus luteum remnants.

In certain animal species, and even in man, we encounter POLYOVULAR FOLLICLES which contain several ova, or ANOVULAR FOLLICLES in which there are no ova. The latter can arise due to the formation of follicles without germinal cells or due to subsequent selective degeneration of the ova in follicles which were originally normal. Although the ovum is essential for the normal maturation of the follicle, the existence of anovular follicles shows that granulosa and theca can develop to some extent without the egg-cell

The Corpus Luteum. — *Immediately* after the discharge of the ovum with its cumulus *oophorus*, the remaining granulosa cells, which line the cavity of the follicle, undergo considerable hypertrophy. Both their nucleus and cytoplasm are enlarged There is also some hyperplasia, but judged by the scarcity of mitotic figures at this time, formation of new cells plays a secondary rôle in increasing the corpus luteum mass. The transformed granulosa layer is thrown into folds, since it becomes *too large to fit smoothly into the follicular cavity*. Hence, the cavity of the follicle becomes star-shaped when viewed in cross section. At the same time, the theca interna cells undergo a similar process of hypertrophy and transformation into corpus luteum cells. *From the outside they invade the spaces* between the granulosa-layer folds and bring *blood vessels into the granulosa*, which originally had no vascular supply. At a later stage, the differentiation between "granulosa corpus luteum cells" and "theca corpus luteum cells" or "paraluteal cells" may become impossible, although for a certain time, those derived from the theca are somewhat darker and poorer in lipids than *those derived from the granulosa*. By far the greater part of the mature corpus luteum is of granulosa-cell origin.

The typical CORPUS LUTEUM CELL differs from the granulosa cell in that it is larger, and has a well-developed, polyhedral cytoplasm which contains numerous lipid granules, cholesterol esters, granules of vitamins A and C as *well as the lutein, a pigment which gives* this structure its characteristic yellow color. *The nucleus* becomes vesicular and possesses a coarse chromatin network with one or two nucleoli. The corpus luteum cells strikingly resemble those of the adrenal cortex and also to some extent, the Leydig cells of the testis. This morphologic similarity is all the more noteworthy since these three types of cells produce chemically *closely allied steroid hormones*

The CAVITY of the original follicle *gradually* becomes organized from the theca, which eventually penetrates across the granulosa to the central cavity Here it forms a loose gelatinous

connective tissue which covers the inner surface of the cyst wall. It leaves some free space in the center which is filled with remains of liquor folliculi, serum and usually some decomposing erythrocytes, remnants of the minute hemorrhages which often accompany the process of ovulation.

The STROMA of the corpus luteum consists of a fine reticular network, in which sinusoids course radially from the periphery towards the center, between the corpus luteum cells.

Many histologists strictly differentiate between the various STAGES IN THE PROCESS OF CORPUS LUTEUM FORMATION. There is a *stage of proliferation and hyperemia* immediately following ovulation. As the name implies, this is characterized mainly by the proliferation and vascularization of the granulosa-cells accompanying the invasion of theca cells.

Secondly, there is the *stage of full development*, in the case of a regular 4-weeks-cycle, between the 17th and 26th day after the beginning of the last menstrual period. Macroscopically, this is characterized by the presence of a glassy, jelly-like coagulum in the central cavity, with a thin, red zone of incretory cells surrounding it At this time the folded glandular layer measures only about 250 to 350μ in thickness. Histologically, the prevalent cellular element is the mature corpus luteum cell with a diameter of 25-40μ and a cytoplasm containing very fine, dust-like lipid granules. In many animal species, the follicular rupture point (the "Blutpunkt" of the German investigators) remains visible on the surface of the corpus luteum in the form of a conically elevated point covered by a blood coagulum.

The third phase in the life of the corpus luteum is the *stage of involution* It begins a few days before the menstrual bleeding and proceeds so rapidly that within 14 days after menstruation, the diameter of the corpus luteum decreases to a few mm. and after six weeks, it is of microscopic size. At first the lipid granules, in the involuting corpus luteum cells, become coarse (storage instead of secretion?), but later they disappear completely and eventually connective tissue replaces the epithelium. Small hemoglobin-pigment-containing, hyalinized connective tissue scars persist for years after the involution of the corpus luteum. These correspond to the scars of atretic follicles Thus in one young woman, who died 5 years after puberty, the number of corpora albicantia found upon histologic examination, corresponded to the number of her menstrual cycles.

The corpus luteum of pregnancy and that of pseudopregnancy (the latter develops only in certain animal species) are larger and persist for a longer time than those of menstruation. (See: Pregnancy, Lactation, Nervous Stimuli, on pp. 334, 381, 383)

Stroma. — The CONNECTIVE TISSUE stroma of the human ovary consists of a network of reticular, elastic and collagenous fibers with fusiform cells resembling fibroblasts. True *smooth muscle cells* have also been described especially in the theca externa of the follicles in certain animal species (e g., sow). The medulla is composed chiefly of loose connective tissue with *elastic fibers* and strands of smooth muscle cells accompanying the blood vessels.

Among the common fibroblasts are some, the so-called "INTERSTITIAL CELLS" of the ovary, which under ordinary conditions may not be distinguishable from fibroblasts However, gonadotrophic hormones stimulate these cells selectively, so that they assume an epithelioid appearance and produce ovarian hormones (see below). In certain animals (e g, rabbit) these cells are extraordinarily numerous

They are probably derived from the theca of atretic follicles and in a certain sense are homologous to the interstitial cells of the testis. However, the sympathicotropic cells (see below) are even more closely related to the testicular Leydig cells. The entire system of interstitial cells is sometimes referred to as the "interstitial gland" or "puberty gland" of the ovary.

In the hilus of the ovary or the mesovarium, certain nests of large, epithelioid cells are found in intimate contact with bundles of non-myelinated nerve fibers. They have been termed SYMPATHICOTROPIC CELLS (*Berger*): extraglandular, interstitial or Leydig cells of the ovary (*Kohn*); Berger cells or hilus cells. Their number and size are subject to great variations. They do not give typical chromaffin reactions and hence should not be considered as paraganglionic elements, but rather as the ovarian equivalents of the testicular Leydig [illegible] to those found in Leydig cells. Their relationship to the latter is also indicated by the fact that their excessive development may lead to virilization.

True CHROMAFFIN CELLS, similar to those of paraganglia, are sometimes also found in the ovarian hilus, but these are essentially different from the "hilus cells."

WALTHARD'S RESTS are cystic or solid structures occurring in the cortex or hilus of the ovary, usually just beneath the lining epithelium. They probably arise from the celomic mesothelium, and may be the primordia from which certain ovarian tumors (Brenner tumors, pseudomucinous cystadenomas) develop. Under normal conditions, they do not seem to have any physiologic function.

Blood Vessels. — The ARTERIES of the ovary are 6-8 small branches originating from an anastomosis of the uterine and ovarian arteries. They enter the gonad through the mesovarium, forming many convolutions. From the hilum, they proceed radially towards the periphery of the organ and split up into capillary networks around the follicles, penetrating the theca, but not the granulosa layer. The corpora lutea are richly supplied with blood vessels in all stages of their development.

The ovarian VEINS course from the perifollicular and stroma capillaries towards the hilus, where they form the cavernous-body-like ovarian plexus.

After puberty, a process of PHYSIOLOGIC SCLEROSIS takes place in the ovarian arteries, apparently due to the stress of constant changes in the nutritive requirements of the ovary during the menstrual cycles, pregnancies, etc. This has variously been referred to as "ovulation sclerosis," "menstrual sclerosis," "partal sclerosis" or "pregnancy sclerosis."

The LYMPHATICS are likewise very well developed in the ovary. Lymphatic capillaries are especially plentiful in the theca externa of the follicles and occur also in corpora lutea and albicantia. The theca interna, granulosa and the albuginea are free of lymphatics.

Nerves. — The sympathetic nerves of the ovarian plexus originate from a ganglionic group which anastomoses with the celiac, renal and mesenteric ganglia. The nerves reach the hilum after a corkscrew-like course through the mesovarium. Then they proceed towards the periphery and distribute their branches to the vessels, stroma, theca and corpora lutea. The granulosa is free of nerves. Sensory fibers ending in Pacini-corpuscles have also been described in the stroma. The existence of a special ovarian "sympathetic ganglion" is doubtful; the ganglion-cell-like elements described by some investigators were probably hilus cells.

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The STROMA of the corpus luteum consists of a fine reticular network, in which sinusoids course radially from the periphery towards the center, between the corpus luteum cells.

Many histologists strictly differentiate between the various STAGES IN THE PROCESS OF CORPUS LUTEUM FORMATION There is a *stage of proliferation and hyperemia* immediately following ovulation. As the name implies, this is characterized mainly by the proliferation and vascularization of the granulosa-cells accompanying the invasion of theca cells.

Secondly, there is the *stage of full development*, in the case of a regular 4-weeks-cycle, between the 17th and 26th day after the beginning of the last menstrual period. Macroscopically, this is characterized by the presence of a glassy, jelly-like coagulum in the central cavity, with a thin, red zone of incretory cells surrounding it At this time the folded glandular layer measures only about 250 to 350μ in thickness. *Histologically, the prevalent cellular element* is the mature corpus luteum cell with a diameter of 25-40μ and a cytoplasm containing very fine, dustlike lipid granules. In many animal species, the follicular rupture point (the "Blutpunkt" of the German investigators) remains visible on the surface of the corpus luteum in the form of a *conically elevated point covered by* a blood coagulum

The third phase in the life of the corpus luteum is the *stage of involution* It begins a few days before the menstrual bleeding and proceeds so rapidly that within 14 days after menstruation, *the diameter of the* corpus luteum decreases to a few mm. and after six weeks, it is of microscopic size. At first the lipid granules, in the involuting *corpus luteum cells*, become coarse (storage instead of secretion ?), but later they disappear completely and eventually connective tissue replaces the *epithelium. Small hemoglobin-pigment-*containing, hyalinized connective tissue scars persist for years after the involution of the corpus luteum. These *correspond to the scars of atretic* follicles Thus in one young woman, who died 5 years after puberty, the number of corpora albicantia found upon histologic examination, corresponded to the number of her menstrual cycles.

The corpus luteum of pregnancy and that of pseudopregnancy (the latter develops only in certain animal species) are larger and persist for a longer time than those of menstruation. (See : Pregnancy, Lactation, Nervous Stimuli, on pp 334, 381, 383.)

Stroma. — The CONNECTIVE TISSUE stroma of the human ovary consists of a network of reticular, elastic and collagenous fibers with fusiform cells resembling fibroblasts. True *smooth muscle cells* have also been described especially in the theca externa of the follicles in certain animal species (e g, sow). *The medulla* is composed chiefly of loose connective tissue with *elastic fibers* and strands of smooth muscle cells accompanying the blood vessels

Among the common fibroblasts are some, the so-called "INTERSTITIAL CELLS" of the ovary, which under ordinary conditions may not be distinguishable from fibroblasts However, *gonadotrophic hormones* stimulate these cells selectively, so that they assume an epithelioid appearance and produce ovarian hormones (see below). In certain animals (e.g., rabbit) these cells are extraordinarily numerous

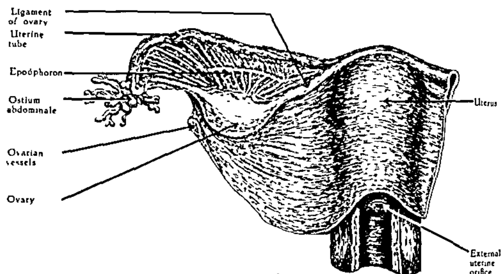


Corpus luteum of the menstrual cycle (Man). — Corpus luteum a few days prior to menstruation. Note that entire right part of the ovary is occupied by the highly corrugated corpus luteum. The hilum is at the left. (Courtesy of Dr. W. Bonn.)





Corpus luteum of the menstrual cycle (Man). — A. Light, large, granulosa corpus-luteum-cells which form a convoluted layer. Surrounding them and between the convolutions, the stroma contains smaller, dark thecal corpus-luteum-cells. The central cavity is partly organized by loose connective tissue (very light). — B. Borderline between small (theca) and large (granulosa) corpus-luteum-cells. The latter contain no hyaline inclusions (such as are supposedly characteristic of gestation). (Courtesy of Dr. W. Bonn.)



Posterior aspect of internal female sex organs





Ovary of newborn (Man). — **A.** Cortex of ovary under low magnification Note irregularities of surface with invaginations of germinal epithelium The large egg-cells are very prominent, but have not yet surrounded themselves with a stratified granulosa layer and no mature follicles are visible — **B.** Same section under higher magnification Note large vesicular nuclei in egg-cells and surrounding stroma Differentiation of granulosa and theca not yet evident.

(Courtesy of Dr W Bonin)

COMPARATIVE MORPHOLOGY

Demonstrably endocrine cells have not been proven to exist in the ovaries of INVERTEBRATES. Large, so-called interstitial cells persist after discharge of the egg in the ovarian region of some species (e.g., hydra) but their function is not known.

In certain viviparous FISH the spent follicles bear some resemblance to the mammalian corpus luteum, but their possible endocrine function has not yet been adequately studied.

Morphologic similarities between certain cell-groups in AMPHIBIAN ovaries and endocrine elements are of doubtful physiologic significance. In some toads there is a small structure, *Bidder's organ*, in the vicinity of the ovary. Morphologically it resembles ovarian tissue and after ovariectomy it can substitute for the loss of ovarian incretions.

Among the REPTILES, certain viviparous Brazilian snakes (crotalus terrificus, bothrops jararaca) form corpora lutea whose physiologic function is clearly shown by the fact that their removal causes abortion, preventable by luteoids.

In most genera of BIRDS, ovulation occurs only from the left gonad, while the right ovary is rudimentary and contains testis-like elements. On the other hand in the hawk, falcon and many other birds of prey, both ovaries are normally developed and participate in egg production, although the right gonad may be somewhat smaller than the left. Certain cell-proliferations in spent follicles resemble corpora lutea, but are of questionable endocrinologic significance.

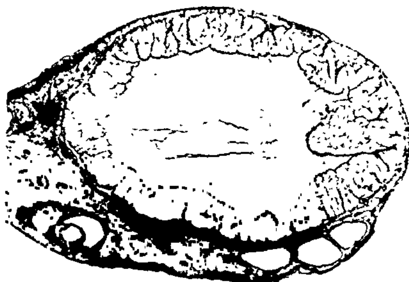
It must be kept in mind that the main object of the corpus luteum is to prepare the endometrium for the reception and maintenance of an embryo. Oviparous species (e.g., birds), which produce eggs containing large amounts of yolk, do not require such maternal trophic influences since nourishment is derived from the yolk-sac. There are close functional analogies between the egg-yolk and the corpus luteum.

The ovaries of all MAMMALS are essentially similar: they have follicles, corpora lutea and varying amounts of interstitial-cell tissue. The number of corpora lutea formed at each cycle differs in the various species: in man, usually only one, rarely two or more, ova are liberated at each cycle; in the rat, the number of ovulating follicles is about 8; in one curious, small South African mammal "elephantulus myurus jamesoni" up to 60 or more. Elephantulus is also noteworthy for having corpora lutea of an unusual type since the granulosa is everted through the rupture point. This process occurs only as a rare anomaly in women and is referred to as "corpus luteum prolapse."

EMBRYOLOGY

In man, the primordium of the gonad can first be distinguished in a ridge called the UROGENITAL FOLD. The latter contains both the genital and the mesonephric (kidney) primordia. The germinal epithelium covering this region continually thickens and protrudes into the celomic cavity mediad to the gradually separating mesonephric fold. At the same time (as early as the 3.5 mm stage), in the caudal end of the embryo, large cells appear which migrate through the dorsal mesentery into the genital fold. The nuclear structure of these so-called primitive or PRIMORDIAL GERM CELLS reveals that even those which are still outside the gonad are true sex cells. It has been thought that these are the source of all definitive germ cells, but most contemporary embryologists believe that the definite ova arise directly from the sex cells of the germinal epithelium and that the primordial germ cells degenerate.

In the six-week-old human embryo, sex can not yet be identified. The surface of the gonad is covered by a germinal epithelium, while most of its substance consists of an inner epithelial



Corpus luteum of pregnancy (Man). — *Corpus luteum during first month of pregnancy* Note corrugated surface of corpus luteum wall and large cavity filled with colloid. The remaining ovarian tissue is atrophic and contains only a few medium-sized follicles The hilum is at the left. (Very low magnification)

(Courtesy of Dr W Borin)





Corpus luteum of pregnancy (Man). — A. Note marked difference between large, granulosa corpus-luteum-cells and small, thecal corpus-luteum-cells The latter fill out the triangular *space* between the convolutions of the former — B. Higher magnification of the borderline between thecal and granulosa corpus-luteum-cells Note dark homogeneous hyaline inclusion in one of the granulosa corpus-luteum-cells (arrow). These are allegedly characteristic of gestation

(Courtesy of Dr W Borin)

Table illustrating probable development of gonadal structures and tumors which may arise from them in the female

(After H. Selye, "Ovarian Tumors," *Encyclopedia of Endocrinology*, 1946.)

Embryonic Structure	Mature Structure: In Male	Mature Structure: In Female	Tumor to which it may give rise in the Female
Germinal epithelium	Seminiferous tubules	Ova and follicles	All types of *serous cysts, papillomas* and *carcinomas*?
Primary germinal cords	Seminiferous tubules	Medullary cords	*Archenoblastomas, mixed teratoids* (by parthenogenesis)?
		Rete of ovary	*Rete adenomas, rete cysts* Brenner tumors?
	Leydig cells	Leydig cells	*Leydig* (or hilus) *cell tumors*
Secondary germinal cords	Seminiferous tubules	Ova and follicles	*Folliculomas, corpus luteum tumors* *Mixed teratoids* (by parthenogenesis)? All types of *pseudomucinous cysts* and *carcinomas* (by parthenogenesis as "pure enteroid teratoids")? *Brenner tumors* (from Walthard's rests or parthenogenetically as abnormal 'enteroid' teratoids)? *Struma ovarii, rhabdomyomas, chorionepitheliomas, false seminomas*, etc. (by parthenogenesis as pure one-sidedly-developed teratoids)
	Testis stroma	Ovarian stroma	*Fibromas, sarcomas*
Pronephros?	Appendix of epididymis	Hydatid of Morgagni and Kobelt's tubules	*Cysts of infundibulum tubae* *Cysts of Kobelt's tubules*?
Urogenital junction tubules	Connection between rete and epididymis	Absent	*Junctional cysts*
Wolffian body (cranial part)	Ductuli efferentes of epididymis	Epoophoron (Epi-oophoron, par-ovarium organ of Rosenmuller)	*Cysts, adenomas* and *carcinomas of epoöphoron-mesonephromas*? Epithelioma Wolffien'?
Wolffian body (caudal part)	Paradidymis	Paroöphoron (Pareooophoron)	*Cysts, adenomas* and *carcinomas* of *paroöphoron*
Wolffian duct (cranial part)	Duct of epididymis	Duct of epoöphoron	*Cyst of Kobelt's tubules*?
Wolffian duct (caudal part) = Gartner's duct	Duct of epididymis	Gartner's duct remnants	*Gartner's duct adenomas*
Müllerian duct (cranial part)	Appendix testis	Oviduct with infundibulum (accessory tubal ostium, tubal diverticulum)	All types of *serous cyst papillomas* and *carcinomas*, ("salpingiomas") Ca of Fallopian tube, *para-ovarian cysts* due to hydrosalpinx of accessory tubal ostium or diverticulum
Mullerian duct (caudal part)	Utriculus prostaticus	Uterus and vagina	*Endometriosis*, (tumors of uterus and vagina not to be discussed here)
Adreno-cortical primordium	Accessory adrenal cortex in region of testis	Accessory adrenal cortex in region of ovary	*Hypernephroma ovarii*

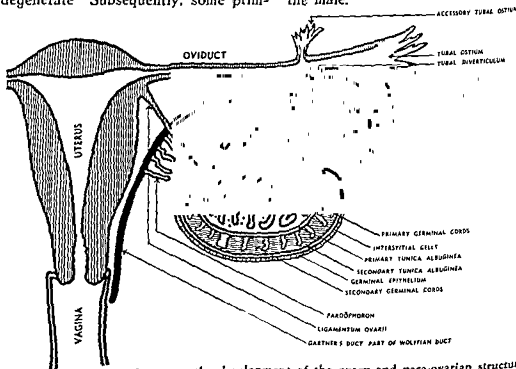
mass derived from an ingrowth, the so-called "*first proliferation*," of germinal epithelium.

In the seven-week-old (13 mm.) embryo, the testes begin to be recognizable, because of the differentiation of cord-like structures, but the ovary has not yet acquired any distinguishing characteristics. It is not until the eleventh week that a dense cortex begins to separate from a loose medullary zone, while in the mesovarium the primitive rete appears. During the third month, stroma and blood vessels invade the ovary from the hilus and the connective tissue septules eventually reach the tunica albuginea. Simultaneously, beginning at the center, most of the cells of the inner epithelial mass are transformed into young ova. In fetuses of three to five months there is rapid ovarian growth, because a new cortical zone is formed, mainly as a result of a "*second proliferation*" of the germinal epithelium. While new ova are formed at the periphery of the gonad, the more centrally located germ cells degenerate Subsequently, some primitive sex-cells of the germinal epithelium (the future ova) surrounded by undifferentiated lining cells (the future granulosa) invade the cortex, thus producing PRIMORDIAL FOLLICLES. The theca cells are probably mainly of mesenchymal origin. It is possible, however, that derivatives of the celomic epithelium remain in the stroma and are transformed into theca cells.

The DESCENT OF THE OVARY from the kidney region into the pelvis is accomplished mainly by the cephalad elongation of the trunk in comparison with the fixed gonad This produces a relative shift of the ovary caudad.

The RETE OVARII is a vestigial organ homologous to the testis. It may persist in the adult and can give rise to rete cysts and adenomas (see: Ovarian tumors).

The EPOOPHORON is a rudiment developing from a cranial group of mesonephric tubules and corresponds to the epididymis: the PAROOPHORON arises from the caudal group of these tubules and corresponds to the paradidymis of the male.



Schematic drawing illustrating the development of the ovary and para-ovarian structures
(After H Selye: "Ovarian Tumors," Encyclopedia of Endocrinology, 1946)

spring during any one pregnancy is also fairly constant. This is referred to as "the law of constant numbers in ovulation" (*Lipschutz*). It is probably due to a species-specific, constant relationship between hypophyseal gonadotrophic hormone secretion and ovarian development. If one ovary is removed, the contralateral gonad tends to produce twice the normal number of ova at each ovulation, thus compensating for the loss. Presumably, a decreased ovarian hormone production (due to the unilateral ovariectomy) automatically occasions a compensatory increase in hypophyseal gonadotrophin secretion. In agreement with the conception that the number of maturing follicles depends upon pituitary stimuli, treatment with exogenous gonadotrophins increases the number of ovulating follicles beyond that expected on the basis of the law of constant numbers

To illustrate this point, in a rat whose two ovaries would produce an average of 12 ova at each cycle, unilateral ovariectomy so influences the remaining gonad that it alone will produce approximately this number. On the other hand, treatment with hypophysoid gonadotrophins may lead to simultaneous ovulation from several dozens of maturing follicles.

Which cell produces which hormone? — FOLLICULOIDS are normally produced by the maturing follicles. This is shown by various observations Only traces of folliculoid hormones are demonstrable in prepubertal or senile animals whose follicles do not mature Injection of hypophysoid gonadotrophins greatly augments follicle maturation and correspondingly induces folliculoid hormone secretion Hypophysectomy, which prevents the maturation of follicles, inhibits folliculoid hormone formation

It is much more debatable whether the granulosa or the theca cells are chiefly responsible for folliculoid hormone formation. In large ovaries (e g., those of cattle) the parts of the follicle can be separated and direct bioassays indicate that follicular fluid, granulosa and theca tissue all contain very high concentrations of folliculoids Destruction of all granulosa cells by X-rays (to which these cells are particularly sensitive) does not produce anestrus in mice if the theca cells are preserved. Treatment of hypophysectomized rats with pure LH fails to stimulate the granulosa, but causes marked proliferation of the theca accompanied by manifestations of estrus These findings clearly indicate that the theca cells are capable of folliculoid hormone production Ovarian tumors consisting of granulosa cells (folliculomas) or theca cells (thecomas) both cause manifestations of marked folliculoid hormone overdosage.

In view of these facts and of the close embryologic relationship between theca and granulosa, it is possible that both these parts of the follicle participate in the secretion of folliculoids, but since the granulosa is not vascularized at least the raw-materials for these hormones must come from the surrounding theca. It should be kept in mind furthermore that *FSH* causes granulosa proliferation without stimulating folliculoid secretion, while *LH* augments the production of folliculoids without affecting the granulosa. The bulk of evidence favors the view that the theca is the source of folliculoids. However, the corpus luteum, testis, adrenal cortex and placenta are also capable of folliculoid production, so that the elaboration of these hormones is certainly not the monopoly of any one cell type.

In the ovary, LUTEOIDS are apparently produced exclusively by the corpora lutea Progestational changes occur in the endometrium only in the presence

THEORIES CONCERNING THE HISTOPHYSIOLOGY OF THE OVARY

In considering the histophysiology of the ovary, it must be kept in mind that we are dealing with an organ having both exocrine (production of ova) and endocrine (production of ovarian hormones) functions. Normally these two activities are coordinated, but under abnormal conditions ovulation is not necessarily accompanied by normal folliculoid and luteoid hormone formation and conversely, the cyclic production of these ovarian hormones may proceed even in gonads whose ova have been destroyed, or fail to be discharged at ovulation.

The Mechanism of Ovulation. — The mechanism of ovulation is still incompletely understood. It is probable, however, that under the influence of the continuously increasing intrafollicular pressure caused by the accumulating follicular fluid, the subcapsular wall of the follicle becomes so thin that it eventually ruptures. Just beneath the cumulus oophorus, the granulosa cells degenerate even prior to ovulation, so that the ovum with the corona radiata is then but loosely attached to the follicular wall. Hence the sudden decrease in intrafollicular pressure, occasioned by the rupture of the wall, readily detaches the ovum with its cumulus and flushes it out through the rupture point with the follicular fluid. The small hemorrhages, which sometimes accompany ovulation, may also be ascribed to the sudden decrease in intrafollicular pressure. It is possible that the smooth muscle cells of the ovarian stroma and theca may help to elicit follicular rupture, especially in those species in which such cells are plentiful

The accumulation of follicular fluid and the final maturation of the follicles and ova are due to gonadotrophic hormones. Hence they are prevented by hypophysectomy and can be elicited at will by gonadotrophins, both in immature and hypophysectomized animals (in which follicle maturation would normally not occur).

The secretion of the follicular fluid is presumably a function of the granulosa cells, since it fails to occur in follicles whose granulosa has been destroyed (e.g., X-rays). On the other hand, the granulosa itself contains no blood vessels, so that the material for the formation of follicular fluid must reach it from the theca interna.

Migration of the Ovum. — After ovulation, the human ovum is discharged into the peritoneal cavity. However, laparotomy performed at that time reveals that the fimbriæ of the Fallopian tubes usually attach themselves closely to the ovarian surface when a follicle is about to rupture and hence the egg tends to enter directly into the oviduct Under abnormal conditions however, the ovum may lose its way and implant itself anywhere in the pelvic peritoneum, thus giving rise to ectopic pregnancy. In certain animals (e g , rat), the ovary is enveloped by a closed ovarian capsule which opens directly into the oviduct and does not communicate with the peritoneum. This obviates the possibility of peritoneal implantation

In women in whom one ovary has been removed, ectopic pregnancy may occur in the tube of that side Here we are evidently dealing with a TRANSMIGRATION OF THE OVUM from the contralateral ovary. Similarly, in animals having two separate uterine horns, removal of one ovary does not preclude the possibility of implantation in the ipsilateral uterus. Some investigators believe that both internal (transuterine) and external (transperitoneal) transmigration of the ovum are possible

The Law of Constant Numbers in Ovulation. — With but minor variations, each species produces a certain, rather constant, number of ova at each ovulation Hence the number of off-

tant rôle in the discharge of the lipid granules (e.g., from the corpus luteum *and theca); these are presumably the* solvents in which the ovarian steroids are stored. Phosphatases, especially adenosine triphosphatase (ATP-ase) — the adenosine triphosphate splitting enzyme important in energy-requiring *reactions of tissues (e.g., muscles) —* is found in comparatively high concentrations in corpora lutea. In general, the ATP-ase activity per unit weight is lower in functional than in non-functional corpora lutea. Among other enzymes, *proteases, arginase, asparaginase,* estrinase, oxidases and glycolytic enzymes appear to be most important.

Ovarian tissue is also comparatively *rich in various* VITAMINS, *especially* vitamin-C, but their function has not *yet been determined.*

Several OTHER METABOLITES (choline, glutathione, citric acid, avidin, *various amines, purines, amino-acids* and thymonucleic acid) have been claimed to play a more or less important part in the chemical composition of ovarian tissue, but their physiologic *rôle is incompletely understood.*

CHEMISTRY OF THE OVARIAN HORMONES

All the ovarian hormones known to date are steroids. Their fundamental chemical characteristics have been described in the section "The Steroids."

GENERAL PHARMACOLOGY OF THE OVARIAN HORMONES

STANDARDIZATION

The direct gravimetric determination *of folliculoids can only rarely be em*ployed because of the minute quantities present in body fluids and tissues. The most commonly used methods are based upon chemical or biologic determina*tions of varying degrees of specificity* and accuracy. These are usually performed on partially-purified extracts containing the desired fraction. Be*cause of the differences in the solubil*ities of the various naturally-occurring folliculoids and their excretion products, it is possible to concentrate and purify the total folliculoid activity of body fluids and tissues, and to subdivide it into its constituent fractions (separation of ketonic folliculoids such as estrone, from the non-ketonic such as estradiol *and estriol, differentiation* between free and conjugated folliculoids, etc.) The conjugated folliculoids are usually biologically less active and more *water-soluble than the free com*pounds, while the latter are more fat-soluble. By acid hydrolysis it is readily possible to transform the conjugated into the free type. At an alkaline pH, however, even free folliculoids are quite *soluble in water because their acid phe*nolic hydroxyl groups form water-soluble salts with alkali.

Analytic Methods for the Detection of Folliculoids. — A number of analytic methods have been devised for the quantitative estimation of folliculoids, but these are useful only when comparatively large amounts are present, as *in the urine of pregnant women.* The most commonly employed analytic methods are the following:

(1) The COLORIMETRIC TESTS are *based upon the observation of Wieland* et al. (1929) that impure folliculoid concentrates prepared from human pregnancy urine, give a yellow color when treated with concentrated sulfuric acid and chloroform (*Salkowski* test). A reddish color with green fluorescence (*Liebermann-Burchardt* test) is obtained when they are treated with *acetic anhydride and sulfuric acid.* Subsequently, *Kober* (1931) showed that the initial orange color, produced by estrone and sulfuric acid, changes to a

of functional corpus luteum tissue. Extirpation of the corpora lutea causes a breakdown of the progestational endometrium even if the remaining ovarian tissue is preserved. However, some evidence indicates that certain extra-ovarian tissues, especially the adrenal cortex and placenta, can also produce luteoids.

The maintenance and function of the corpus luteum depends upon stimulation by the *luteotrophic hormone* of the anterior-pituitary or placenta. Hypophysectomy causes a breakdown of a functional corpus luteum unless a fairly mature placenta is present in the organism or luteotrophic hormone is administered.

The *lipid granules* in the corpus luteum and theca cells are probably carriers of the (highly lipid-soluble) ovarian hormones.

There is no evidence that either the afferent or the efferent *nerves* of the ovary play any important rôle in the formation of ovarian hormones, since denervated ovaries or transplanted ovaries (whose nerves are of course severed) continue to form hormones under the influence of gonadotrophic hormones. (See also: Stimuli Influencing the Ovary, pages 381, 382.)

CHEMISTRY OF THE OVARIES

CHEMICAL COMPOSITION OF THE GLAND

The chemistry and biogenesis of the ovarian hormones will be discussed in subsequent chapters. Here, we shall merely consider the most important data concerning the general chemical composition of the gland

It is difficult to make generalizations concerning the chemical composition of ovaries, because of the marked structural changes which they undergo between childhood and senility, as well as during each sexual cycle in the adult

In general it may be said however, that the CARBOHYDRATE content of the ovaries is comparatively low, although traces of glycogen and lactic acid are demonstrable in them.

The LIPID content of the corpora lutea is especially high, but in the remaining parts of the ovary it is rather low. It appears that the *phospholipid* concentration rises in the corpora lutea until about the 10th day after ovulation, following which it begins to diminish. Conversely the *cholesterol* ester content — which indicates involution — is low until the 10th day and then rises suddenly. The corpus luteum also contains rather considerable amounts of *neutral fats* and *fatty acids;* the quantity of these is comparatively low during the most active phases, but rises when involution begins. On the other hand, the scars of corpora lutea are almost completely devoid of lipids

The bright yellow pigment so characteristic of the human corpus luteum is generally referred to as *lutein.* It belongs to the lipochromes or lipid pigments and is probably similar to the yellow pigment of egg yolk, but it has not yet been clearly characterized It is presumably closely related to the vegetable pigments, carotene and xanthophyll, both of which have been demonstrated in corpus luteum tissue. A large percentage of the corpus luteum lipids occurs in the ovary in combination with protein as lipoprotein

The major part of the dry material in ovarian tissue is PROTEIN, but so far the characteristics of the ovarian proteins have not been adequately studied.

Among the INORGANIC CONSTITUENTS, sodium, chloride and potassium are most important; but bromine, iodine, sulphur, iron and copper are also present

Various ENZYMES occur in comparatively high concentrations in ovarian tissue Lipases appear to play an impor-

or to effect quantitative hydrolysis of the conjugate and determine the free compound as such.

Bioassay of Folliculoids. — The INTERNATIONAL UNIT (I.U.) of folliculoid activity is by definition that equivalent to the folliculoid potency of 0.1γ of pure estrone under the same bioassay conditions. It is therefore recommended to use estrone as a reference standard in such assays. The INTERNATIONAL BENZOATE UNIT (I.Bz.U.), which is equivalent to the activity of 0.1γ of estradiol-3-monobenzoate, has been recommended as a standard for the assay of slowly-acting folliculoids.

For the determination of folliculoids in body tissues and fluids, bioassays are usually more satisfactory than chemical methods of determination since they are more specific and can be performed with less completely purified material, minimizing losses during the process of purification.

In principle, BIOPSY SPECIMENS taken from patients (e.g., endometrium, vaginal smear) represent "internal bioassay technics" obviating the necessity for chemical purification of the folliculoids. The responses of the donors' tissues (e.g., follicular-phase endometrium, vaginal cornification) are themselves the indicators of hormone action. The great advantage of these procedures — as of all internal bioassays — is that they indicate the activity of hormones under the conditions existing in vivo. Their interpretation is less likely to be blurred by such factors as changes in the renal threshold for the hormones, variations in the degree of destruction and detoxification after the hormones have exerted their normal effects, transient fluctuations in hormone production and especially losses during extraction for bioassay. On the other hand, these methods are fundamentally qualitative and permit only an approximate estimation of the amounts of hormones present.

The technics devised for the bioassay of folliculoids in body fluids and tissues are usually based upon their extraction from the biologic material and the study of their effects upon sensitive test objects. The following are the most commonly used procedures.

(1) The ALLEN-DOISY TEST (1923) and its various modifications, is performed on immature or spayed mice or rats, whose vaginal epithelium is not cornified. Repeated subcutaneous injection of folliculoids into such test-animals [illegible] cytes an[illegible] one or two days [illegible]ed by the histologic examination of stained (or even unstained) vaginal smears. Since spayed animals which have not been used for such tests for some time become insensitive, it is essential that prior to the test they be sensitized by a preliminary injection of a minimal effective dose of a folliculoid. The sensitivity of this assay may be increased by partial hepatectomy, since the liver inactivates much of the injected folliculoids. If the duration of action of a folliculoid is to be measured (e.g., prolongation of action by esterification) a single subcutaneous dose is administered and the length of the induced vaginal estrus is measured by taking vaginal smears bi-daily for several days.

(2) The METROTROPHIC TEST (Astwood, 1938) is performed on immature female rats (25-49 gm.) receiving a single subcutaneous injection of the folliculoid. The animals are killed 6 hours later and the increase in the weight of the uteri is taken as a criterion. The advantage of this test lies mainly in its rapidity.

(3) In EMMENS' S/L TEST (1940) two groups of spayed mice are given folliculoid by the subcutaneous and intravaginal route respectively. The criterion is the presence in the vaginal smears of cornified or nucleated epithelial cells in the absence of leukocytes.

clear green-fluorescing red, when heated with water. In this manner the folliculoids can be differentiated from cholesterol, pregnanediol, bile acids and many other steroids, as these give a yellow color with sulfuric acid and this is decolorized by water. *Cuboni* (1934) used this test for the diagnosis of pregnancy in mares, which excrete large amounts of folliculoids during gestation. *Kober* (1931) also showed that the intensity of the fluorescence may be diminished and the intensity of the red color enhanced by using a mixture of phenol and sulfuric acid instead of the acid alone. This is due to the resulting formation of phenolsulfonic acid. Subsequently, he (*Kober*, 1936) introduced a second modification substituting β-naphtholsulfonic acid for the phenolsulfonic acid, the color being measured photoelectrically

More recently, *Bachman and Pettit* (1941) devised a particularly accurate and sensitive modification of the Kober reaction. Their method permits the quantitative extraction of urinary folliculoids in a form pure enough to yield, with appropriate color-reagents, products closely resembling those obtained with pure crystalline hormones. The procedure also allows the complete separation of estriol from the sum of estrone and estradiol. The technic permits the determination of estriol when this substance is present in the urine in concentrations exceeding 1000γ/L, and the estimation of the sum of estrone and estradiol when it exceeds 500γ L Thus it is practically applicable in the assay of human pregnancy urine after the fourth month of gestation

Alkaline picric acid solutions have long been used for the determination of creatinine (*Jaffe*, 1886). It has been found that similar color-reactions are given by various compounds containing the group — $CO\text{-}CH_2$ —, such as that at C_{17} in estrone. *Zimmermann* (1935) took advantage of this by devising a colorimetric method, in which estrone solutions are treated with m-dinitrobenzene and KOH, whereupon a violet color results. The method is obviously not specific and it cannot be used for the detection of the non-ketonic folliculoids (estradiol and estriol) which do not contain the above grouping. However, under certain experimental conditions, the test can differentiate between ketonic testoids and ketonic folliculoids since, as previously mentioned, the latter are phenolic and can be removed from fat-solvents by extraction with alkali, leaving the neutral ketonic testoids behind.

(2) The characteristic ULTRA-VIOLET ABSORPTION spectrum of estrone (maximum absorption at about 2820 Å with a well-marked minimum at about 2500 Å in neutral or acid solution; and a maximum at 2950 Å with a corresponding shift of the minimum in alkaline solution) and of other folliculoids may also be used for analytic purposes, but only highly purified samples are suitable for spectrography and hence this is not yet practical for routine use.

Analytic Methods for the Detection of Luteoids. — There are no practical methods for the determination of progesterone in biologic material, but its chief excretion product, pregnanediol, can be detected in the urine (though not in the blood) by gravimetric methods *Venning* (1937) developed such a method which permits the determination of pregnanediol-sodium-glucuronidate This is expressed in terms of free pregnanediol by calculation *Bucher and Geschichter* (1940) described a technic which permits separate recovery and estimation of the free and combined forms from the same urine specimen. It is doubtful, however, whether free pregnanediol occurs naturally i the urine, most of it certainly arises du to spontaneous hydrolysis of the con jugate after voiding. Hence care must be taken either to prevent hydrolysis,

urine. However, space does not permit the detailed discussion of this and the many additional methods recommended for the quantitative analysis of folliculoids in biologic material.

Bioassay of Luteoids. — The INTERNATIONAL UNIT of luteoid potency is defined as the activity corresponding to that of 1.0 mg. of progesterone under the same bioassay conditions.

Among the many bioassay technics used for the estimation of luteoids in solution, the following deserve special attention :

(1) IN THE CORNER AND ALLEN TEST (1929) adult female rabbits are spayed 18 hours after having been mated during estrus The substance to be tested is then injected subcutaneously, daily for 5 days. The minimum amount necessary to cause complete progestational proliferation of the endometrium is taken as a unit. This is equivalent to 1 25 mg. of progesterone.

(2) THE CLAUBERG TEST (1930) is a modification of the former in which intact immature rabbits (pretreated with 8 daily injections of folliculoids) are used. The luteoid substance to be tested is subsequently given in 5, daily, subcutaneous injections and the total dose necessary to produce a "definite" progestational transformation of the endometrium is taken as the unit. This corresponds to 0.75 mg. of progesterone.

(3) THE MCPHAIL TEST (1934) is performed on immature female rabbits (750-950 gm) treated with 150 I U of estrone over a period of 6 days, after which the unknown solution of the luteoid is administered in 5, daily, subcutaneous doses. In a clearly defined scale ranging from 0 to ++++ of progestational proliferation, an average reaction of ++ is taken as the unit. This corresponds to 0.25 mg of progesterone

(4) THE PINCUS AND WERTHESSEN TEST (1937) is carried out on rabbits spayed 18 to 20 hours after mating. They then receive bi-daily injections of the luteoid to be assayed, on the 2nd, 3rd and 4th day after copulation. On the 5th day, the animals are killed and the fertilized ova (blastocysts) washed out of the uterus. The luteoid activity is estimated by determining the relationship between the degree of progestational development (measured with a planimeter) and the growth of the fertilized ovum 0 38 mg. of progesterone can be detected with this technic. Various other modifications are based upon the ability of luteoids to maintain gestation in rabbits, which otherwise regularly abort following ovariectomy during gestation

(5) THE TEST OF FEVOLD ET AL. (1930) is based on the ability of certain corpus luteum extracts to cause relaxation of the pelvic ligaments in guinea pigs. The test is supposed to be specific for a special hormone of the corpus luteum ("relaxin"). However, since folliculoids and various mixtures of folliculoids and progesterone induce relaxation of the pelvic ligaments, the specificity of the technic is doubtful.

(6) THE SEXUAL RECEPTIVITY TEST is based upon the fact that ovariectomized virgin guinea pigs, pretreated with folliculoids, exhibit the copulatory reflex (arching and straightening of the back and elevation of the pudenda) following the subsequent administration of luteoids, if the vulvar region is stimulated.

(7) THE VAGINAL MUCIFICATION TEST, performed in mice, guinea pigs or rats, is based upon the observation that immature or castrate females respond with mucification of the vaginal epithelium if luteoids are administered following sensitization with folliculoids Since minute doses of folliculoids in themselves cause similar reactions, the test is not very specific.

(8) THE VARIOUS DECIDUOMA TESTS are based upon the fact that in folli-

The S/L ratio is that between the effective dose of Systemic and Local administration. The test is used for the differentiation of folliculoid precursors from active folliculoids. For the former, the ratio is in the neighborhood of unity, while for the latter it is much greater, since they act directly upon the vaginal epithelium without having to be absorbed and activated in the organism.

Several other indicators, such as the growth of the NIPPLES in male guinea pigs, the lengthening of the OVIPOSITOR in certain fish (bitterling), the feminization of the PLUMAGE in capons, the OPENING OF THE VAGINA in spayed adult guinea pigs, prepubertal mice or rats (in which the vagina is normally closed by a membrane), the MUCIFICATION OF THE VAGINAL EPITHELIUM of the rat (elicited by folliculoids in doses insufficient to cause cornification) and many other characteristic changes caused by folliculoids, have been used for bioassay purposes.

As previously stated, unlike the internal, the external bioassays must be preceded by at least partial chemical purification of the hormones, the hormone concentration in tissues and body fluids is usually not high enough to permit bioassay of the source material (blood, urine, etc.) in its original state. Several methods have therefore been developed for the quantitative EXTRACTION AND SUBSEQUENT BIOASSAY of folliculoids. Among these, the following are most useful:

(1) The BLOOD-FOLLICULOID TEST of *Frank and Goldberger* (1935) which is based upon the fact that in regularly menstruating women, the blood-folliculoid titer rises significantly a few days *before the onset of* bleeding, hence venous blood is taken shortly before the expected period. If the menses are irregular, blood specimens must be obtained weekly for more than a month, in order to detect possible cyclic variations in blood-folliculoid concentration 50 cc. of blood are extracted, according to a certain procedure, and assayed by the Allen-Doisy test.

(2) The BLOOD-FOLLICULOID TEST OF *Fluhmann* (1934). 25-40 cc. of venous blood are taken, immediately centrifuged and 0.5 cc. of the clear serum is injected subcutaneously, 3 times daily, to spayed adult female mice on 3 consecutive days, each animal *receiving a total of 4.5 cc. In this test,* the serum itself can be used without extraction since the slightest degree of vaginal response, the mucification of the atrophic epithelium, is taken as positive. An approximately quantitative estimation is possible, even using only a single dose level, since various degrees of response between mucification and complete cornification can be distinguished with this technic.

(3) In the URINARY FOLLICULOID TEST OF *Kurzrok and Ratner* (1932) the folliculoid activity of the urine is extracted with ethyl acetate in a continuous extractor. Following further purification, the extract is dissolved in oil for bioassay in the Allen-Doisy test

(4) In the URINARY FOLLICULOID TEST OF *Smith and Smith* (1935) the conjugated urinary folliculoids are first hydrolysed and thus transformed into *the free, more active form;* then the total urinary folliculoids are determined. Following concentration and purification, the active material is dissolved in oil and assayed on spayed female rats by the vaginal smear test. This method is superior to those carried out on not-hydrolyzed urine, since the proportion between free and total folliculoids varies and hence, bioassays cannot yield accurate data concerning the total folliculoid elimination unless there is total transformation into the biologically-active form.

Subsequently, *Smith and Smith* (1939) devised a modification for the extraction and separation of estrone, estriol and other folliculoids in the

culoid hormone pretreated animals (rats, guinea pigs) subsequent treatment with progesterone so sensitizes the endometrium that it responds to local trauma by the formation of a deciduoma (maternal placenta tumor).

(9) The inhibition by luteoids of the UTERINE CONTRACTIONS normally produced by oxytocic posterior-pituitary extracts in the rabbit, is not sufficiently specific to serve for bioassay purposes.

(10) The LOCAL APPLICATION OF LUTEOIDS TO THE RABBIT ENDOMETRIUM following folliculoid pretreatment, is one of the most sensitive tests as it permits the detection of as little as 0.5-5.0γ of progesterone. It is a valuable qualitative indicator of luteoid activity, but due to great individual variations in response, its applicability as a quantitative technic is rather limited.

(11) From the clinician's point of view, the most satisfactory bioassay is that based upon the induction of PROGESTATIONAL PROLIFERATION IN THE ENDOMETRIUM OF SPAYED OR POSTMENOPAUSAL WOMEN pretreated with folliculoids. This method gives direct evidence of luteoid activity in man, but for obvious reasons, it is not suitable for accurate quantitative assays on a statistically significant basis.

(12) The "INTERNAL BIOASSAY" of endogenous luteoid production is performed by evaluating endometrial biopsy specimens obtained by curettage.

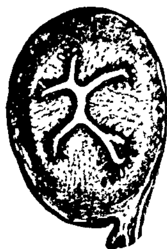
PHARMACOLOGY OF OVARIAN HORMONE DERIVATIVES AND OF ARTIFICIAL OVARIAN HORMONES

Folliculoids and Artificial Folliculoids. — It is not within the scope of this book to discuss the special pharmacology of the numerous natural and artificial folliculoid compounds. It should be emphasized, however, that unlike the derivatives of the other steroid hormone groups (testoids, luteoids, corticoids, renotrophic and spermatogenic steroids) the most potent folliculoids (like some of the most active anesthetic steroids) exhibit their chief activity to the exclusion of all other hormone actions. This is what we defined as a "simple" action. (See: The Steroids.) Even the various artificial folliculoids, many of which are chemically very different from the naturally occurring hormones, exhibit exclusively folliculoid potency. It is interesting, however, that most of the artificial folliculoids possess some anesthetic action as do the corresponding natural compounds. Indeed, some of the amine-substituted dihydrostilbestrol derivatives possess morphine-like analgesic effects, although they exhibit no obvious folliculoid potency.

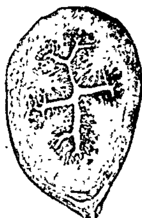
Most of the artificial folliculoids are particularly active by mouth. This represents a great practical advantage over the natural hormones which are comparatively inactive when administered orally. It is noteworthy, however, that certain metabolites of the natural folliculoids such as estriol glucuronide (emmenin) which is present in human pregnancy urine, or estrone sulfate (premarin) from pregnant mare's urine are both orally active derivatives of naturally occurring hormones. The natural folliculoids have been discussed in the section The Steroids. In the following table, we list merely the main characteristics of the most important artificial folliculoids. For the sake of simplicity, folliculoid activity is expressed in international units (I.U.) but the relevant data are only *very approximate* estimates since they are based on bioassays performed in different laboratories under not quite comparable conditions.

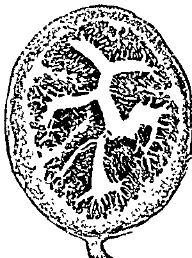
with a folliculoid (note estrus development of endometrium) — C, D, E and F. 1, 2, 3 and 4 plus progestational response in estradiol-pretreated immature rabbits, given increasing doses of progesterone. Note the increasingly more pronounced "lacing" of the six longitudinal folds of the endometrium.













A

B

C

D

E

F

Biossay of luteoid activity in the McPhail test — A Cross-section through the uterus of an immature, untreated rabbit B. Cross-section through the uterus of an immature rabbit, treated

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Most of the artificial folliculoids are particularly active by mouth. This represents a great practical advantage over the natural hormones which are comparatively inactive when administered orally. It is noteworthy, however, that certain metabolites of the natural folliculoids such as estriol glucuronide (emmenin) which is present in human pregnancy urine, or estrone sulfate (premarin) from pregnant mare's urine are both orally active derivatives of naturally occurring hormones The natural folliculoids have been discussed in the section · The Steroids In the following table, we list merely the main characteristics of the most important artificial folliculoids. For the sake of simplicity, folliculoid activity is expressed in international units (I.U.) but the relevant data are only *very approximate* estimates since they are based on bioassays performed in different laboratories under not quite comparable conditions

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Principal artificial folliculoids and some related compounds

Name of Compound	Formula	Characteristics
ETHYNYL-ESTRADIOL [17(β)-ethynyl-$\Delta^{1,3,5,10}$-estratriene-3,17(α)-diol] *Syn* 17-ethinyl-estradiol		I U. = about 0 05γ (subcutaneously). Due to ethynyl side-chain highly active when given by mouth
DOISYNOLIC ACID [16||17-$\Delta^{1,3,5,10}$-estratriene-3-ol-17-carboxy acid]		When assayed as the sodium salt I U. = about 0 1γ (subcutaneously) More active than estrone when given by mouth Note that this and especially the following compound possess great folliculoid activity in spite of the opening of ring D
BISDEHYDRO-DOISYNOLIC ACID [16||17-$\Delta^{1,3,5,10,6,8}$-estrapentaene-3-ol-17-carboxy acid]		When assayed as the sodium salt I U = about 0 01γ (subcutaneously), equally active when given by mouth This is the most active folliculoid substance known to date
DIETHYLSTILBESTROL [4 4'-dihydroxy-α β-diethylstilbene] *Syn* stilbestrol		I U = about 0 05γ (subcutaneously) almost equally active by mouth In women stilbestrol by mouth is about as active as estrone by injection Depending upon the position of the ethyl groups, the compound can exist in two isomeric forms Both formulae given here represent the biologically more active isomer, but the lower formula is written in a manner emphasizing its resemblance to steroids
HEXESTROL [3,4-di(p-hydroxyphenyl)-hexane] *Syn* · dihydrodiethylstilbestrol		I U = about 0 03γ (subcutaneously), almost equally active by mouth In women claimed to be slightly more active and less toxic than stilbestrol
[1-(m-hydroxyphenyl) 3-(p-hydroxyphenyl)-hexane]		I U = more than 20 mg Note that in spite of similarity to steroids the activity is greatly decreased in comparison with stilbestrol, due to the change in the aliphatic block between the phenolic rings

Principal artificial folliculoids and some related compounds (Continued)

Name of compound	Formula	Characteristics
BENZESTROL (2,4-di (p-hydroxyphenyl)-3-ethyl-hexane) *Syn*: octofollin	HO–C₆H₄–CH·CH·CH–C₆H₄–OH	When most active isomer is tested I U. = about 0 04γ (subcutaneously), almost equally active by mouth
DODDS' COMPOUND M4 (β-hydroxy-α,β-diphenyl-n-ethylamine)		Not folliculoid. This and other diphenylethylamines are not only chemically closely related to dihydro-diethylstilbestrol, but also to morphine the formula of which is [formula]. Like morphine and the steroid hormones it possesses anesthetic and analgesic properties
(1 methyl-2 (p-hydroxyphenyl)-6-hydroxy-3 4-dihydro-naphthalene)		When assayed as 6-methyl ether I U = about 0 5γ Naphthalene derivative, distantly related to the steroids. *Allenolic acid derivatives* are also related
(5 6-cyclopenteno-1,2-benzanthracene)		Strongly carcinogenic benzanthracene derivative possessing only trace of folliculoid activity
TRIPHENYLCHLORETHYLENE (α-phenyl-β-chlorostilbene)		I U = about 80γ (subcutaneously), equally active by mouth Note that this, and the above mentioned compound, exhibit folliculoid activity, although they contain no oxygen

Luteoids — Only very few artificial luteoids have been prepared as yet. The most commonly used among them is ethynyl-testosterone It is much less luteoid than progesterone, but has the advantage of oral activity In high doses it is slightly virilizing.

More recently, ethynyl-androstenediol has been used experimentally as an orally active, artificial luteoid It is somewhat less luteoid than ethynyl-testosterone, but considerably less virilizing.

The following table lists the main characteristics of the two most important artificial luteoids For the sake of simplicity, luteoid activity is expressed in international units, but, as in the case of the previous table, the relevant data are only *very approximate*.

Principal artificial luteoids

Name of Compound	Formula	Characteristics
ETHYNYL-TESTOSTERONE [17(β)-ethynyl-Δ^4-*androstene*-3-one-17(α)-ol] *Syn* pregneninolone, pregneninonol, anhydro-hydroxyprogesterone		I.U. = about 10 mg. (subcutaneously), almost equally active by mouth, due to the ethynyl side chain. Possesses some testoid activity but this is very slight in women
ETHYNYL-ANDROSTENEDIOL [17(β)-ethynyl-Δ^5-*androstene*-3(β),17(α)-diol] *Syn* ethynyl-Δ^5-androstenediol-3 17		I U. = about 20 mg (subcutaneously), almost equally active by mouth, due to ethynyl side-chain. Less testoid than ethynyl-testosterone

MODE OF ADMINISTRATION AND CHIEF INDICATIONS

Folliculoids. — In administering folliculoids, it must be kept in mind that the response is subject to great individual variation. Hence the doses recommended are always approximate, they should be adjusted to the individual case by controlling the vaginal smears and other manifestations of folliculoid activity. If systemic effects are desired, oral or parenteral administration is most convenient, but if only one specific target organ is to be affected, topical application may prove preferable.

The cost of prolonged therapy with natural folliculoids is rather high and since the artificial folliculoids (especially those of the stilbene series) are equally effective, preference may be given to them if financial considerations are important However, some patients suffer from nausea following oral treatment with stilbene derivatives. Since in most instances, folliculoid therapy takes the form of repeated short periods of treatment, the implantation of crystal pellets or the injection of crystal suspensions is rarely desirable.

INTRAMUSCULAR or ORAL administration are recommended whenever systemic actions are desired. SUBCUTANEOUS administration of oily solutions is contraindicated because poor absorption leads to accumulations of oil. The average dosage for typical cases of *hypogonadism* with *amenorrhea*, or *suppression of lactation*, varies between 5000 and 50,000 I.U., that is, an activity equivalent to 0.5-5.0 mg. of estrone This corresponds approximately to 2-10 mg of stilbestrol and 0.2-3 0 mg of hexestrol or benzestrol per os. Estrone-sodium-sulfate (premarin) is usually administered orally in tablets containing 1 25 mg The latter compound is less likely to cause nausea than the stilbene derivatives. In most instances, these compounds are given in the above dosages two or three times weekly until the desired effect is obtained, but it is advisable to interrupt therapy every two or three weeks in order to prevent the development of metropathia hemorrhagica If regular menstrual cycles are to be induced, progesterone should be given after interruption of the folliculoid treatment. Ethynyl-estradiol or estriol may also be administered per os in equivalent doses, since they have a comparatively high oral activity. In the therapy of *dysmenorrhea and menopausal disturbances*, the lowest dose levels usually suffice (e g , 0 5-1.0 mg. of stilbestrol per day).

SUBLINGUAL (or buccal) administration has the advantage that the compound is directly absorbed into the circulation without having to pass through the intestinal tract. Thus, destruction by gastrointestinal enzymes is avoided and detoxification in the liver is minimized, since — *unlike after oral administration* — the compound does not pass first through the liver by way of the portal circulation. For this purpose, ethynyl-estradiol, or estradiol itself, is instilled into the sublingual space, in propylene glycol solution, in daily doses of about 0.2-0.5 mg. For routine clinical use this technic is rather impractical since it is inconvenient and — because of variations in absorption rate — it does *not permit* accurate dosage.

RECTAL administration of folliculoids is also *effective* in women, but comparatively inefficient and hence rarely used. About 15 times the subcutaneous dose of natural folliculoids is required when given in this manner.

VAGINAL administration is recommended especially in the therapy of *gonorrheal vulvo-vaginitis* in children, or *senile vaginitis and kraurosis vulvæ* in postmenopausal women. Vaginal suppositories (containing 0.02-0.4 mg of estrone or estradiol or 0.1-0.5 mg of stilbestrol) are recommended for this purpose. These comparatively small doses are effective, because in this case the folliculoids act directly on the target organ and are less subject to destruction in the body.

NASAL application, by a spray, of oily solutions (*10,000-20,000 I.U. per cc.*) of various folliculoids is advisable *in cases of atrophic rhinitis, after irrigating the nose with an alkaline wash in order to remove the crusts*.

Some gynecologists advocate the PERCUTANEOUS use of folliculoids in an ointment base. While there is no doubt that folliculoids can be absorbed through the intact skin, the rate of absorption varies greatly and can not be foretold. This mode of administration may be applicable in cases of *breast-hypoplasia, acne and hypertrichosis*, where local action is desired, but the cosmetic value of folliculoids in various creams and ointments has been greatly overrated. When systemic effects are desired, the percutaneous route of administration *is not to be recommended*.

Direct INTRA-UTERINE application of folliculoids undoubtedly causes a pronounced local effect in experimental animals, indicating that these hormones exert a direct action upon this target organ. In women, the intrauterine application of folliculoid-containing suppositories, or actual injections of folliculoids into the substance of the uterine muscle have been advocated by some, *but this technic is still in the experimental stage*.

INTRASPLENIC, INTRAPERITONEAL AND INTRAHEPATIC application of folliculoids have played an important rôle in animal experimentation, in proving that these hormones are detoxified during their passage through the liver. They are less effective, when given by any of these routes, than when administered subcutaneously or intramuscularly in equivalent doses. In clinical medicine, the above modes of application are, of course, never employed.

INTRAVENOUS injection of *water-soluble folliculoids, would only be justified* if very sudden and transitory effects were desirable. This is hardly ever the case in clinical medicine.

TRANS-PLACENTAL application of folliculoids is also effective, as shown by the fact that if such compounds are injected into pregnant animals typical actions are elicited in the embryos. The comparatively excessive development of the breasts and other accessory sex organs in newborn children, is probably due to such trans-placental absorption of maternal folliculoids.

Direct application of folliculoids to certain areas of the COMB causes a local inhibition of its growth in capons simultaneously treated with testoids

Local injection of folliculoids into the FEATHER FOLLICLE of the fowl induces typical folliculoid changes in the treated feathers only.

Introduction of folliculoids into BONES caused local stimulation of osteogenesis in the duck and pigeon, hence this action is presumably also direct

Luteoids. — Only two compounds of this series are in common clinical use, namely progesterone, which is given parenterally by the INTRAMUSCULAR route, and ethynyl-testosterone, which is given ORALLY. SUBCUTANEOUS administration is not recommended (oil accumulations !). Progesterone is almost certainly the natural luteoid compound produced by the corpus luteum. Ethynyl-testosterone is a synthetic, artificial luteoid, prepared from progesterone or testosterone. It is estimated that progesterone parenterally is equivalent to about 5 times as much ethynyl-testosterone per os

For parenteral administration, progesterone is usually injected daily, or every 2nd-3rd day, in oily solution, in doses varying between 1 and 10 mg In *amenorrhea*, it is given over a 7 day period, following 2 weeks of folliculoid hormone pretreatment; in *dysmenorrhea* and *menorrhagia* 3 to 6 days before the expected flow: in *metrorrhagia* — especially the type due to metropathia hemorrhagica — cyclic administration is recommended 4 doses are given every other day; this is usually followed by withdrawal bleeding and 20 days after the onset of this bleeding, the same 8-day course is repeated In this manner, artificial luteal phases, followed by apparently normal bleedings are produced, and eventually spontaneous cycles may reappear, especially in young women.

Progesterone has also been recommended in approximately the same doses in *sterility* due to inadequate progestational proliferation which interferes with the nidation of the ovum. Here it is administered daily, beginning on the 14th day of the regular cycle or whenever the occurrence of ovulation is suspected. Treatment is continued until the onset of flow (if treatment was ineffective) or until conception occurs and is verified by the Aschheim-Zondek test, or one of its modifications

In *threatened or habitual abortion*, progesterone injections are recommended, daily or every second day, until the danger of miscarriage subsides. The efficacy of the treatment in these cases has not yet been definitely demonstrated, but many of the reported results are encouraging.

Parenteral progesterone administration has also been advocated in the therapy of *hyperemesis gravidarum* and premenstrual tension. In the former instance, it may be given continuously until hyperemesis subsides, while, in premenstrual tension, it is usually administered daily during the week preceding the expected date of the menses

For all these indications, ethynyl-testosterone may be alternatively given by mouth in the form of tablets containing 5-10 mg The main contraindication for ethynyl-testosterone is its virilizing effect, but in women the latter is very slight in comparison with the response of some animals If necessary, the less virilizing but also orally active ethynyl-androstenediol may be tried.

PERCUTANEOUS administration of progesterone or ethynyl-testosterone to the shaved skin of folliculoid-pretreated immature or castrate rabbits, causes typical progestational proliferation of the uterus. This shows the possibility of absorption through the skin. By this route the hormone is particularly active in alcoholic solutions.

SUBLINGUAL OR BUCCAL administration of progesterone is effective in women if the compound is dissolved in propylene glycol.

INTRASPLENIC, INTRAHEPATIC OR INTRAPERITONEAL administration of progesterone is less effective than if the same amount is given under similar con-

ditions by the subcutaneous or intramuscular route. This is presumably due to detoxification during the passage through the liver, and to the fact that from these sites progesterone is especially rapidly absorbed, hence it is eliminated before it could fully exert its luteoid properties.

INTRAVENOUS administration of luteoids is rarely advisable, since in this event detoxification and excretion are too rapid to permit optimum efficacy.

The direct application of progesterone to the ENDOMETRIUM causes a local progestational proliferation, indicating that the compound acts directly upon the uterine lining. Advantage has been taken of this in the bioassay of the compound when only minute doses are available. There are no clinical indications, however, *for any type of topical* application of luteoids.

WITHDRAWAL EFFECTS AND PERMANENT CHANGES CAUSED BY TEMPORARY TREATMENT

After adequate folliculoid treatment, whether or not it is followed by luteoid administration, WITHDRAWAL BLEEDING occurs *from the primate endometrium.* In most of the other vertebrates however, the endometrium involutes without breakdown after hormone withdrawal.

It is also noteworthy that PERMANENT CHANGES MAY BE CAUSED BY TEMPORARY TREATMENT with folliculoids. Thus, *in very immature or embryonic* male animals, excessive treatment with folliculoids *may* cause permanent damage in the testes and accessory sex organs.

OTHER PHARMACOLOGIC PROBLEMS

Other pharmacologic problems concerning the folliculoid and luteoid hormones, as well as their biogenesis and fate in the body will not be reviewed here, since they have been discussed in the section · The Steroids and on p 372.

Suffice it to re-emphasize that both *folliculoids and luteoids appear to be detoxified* mainly in the liver; partly by the formation of conjugates, and partly by oxidation or reduction. Certain folliculoids (e g., estriol) are more active in intact than in spayed animals; this suggests activation in the ovary.

Numerous steroids are comparatively more active upon systemic than upon direct local application to the responsive target organ; this also suggests transformation of *pro-folliculoids* into the fully active folliculoids in some (unidentified) internal organ.

"*Relaxin*" (see p. 345) has been extracted from corpora lutea and pregnancy blood. Unlike folliculoids and luteoids it causes relaxation of pelvic ligaments even after hysterectomy.

EXPERIMENTAL PHYSIOLOGY OF THE OVARIES

EXPLANTATION OF THE OVARIES

Various investigators succeeded in preparing viable TISSUE CULTURES of ovarian parenchyme in a variety of media. Not only the stroma, but even the epithelial elements, especially the granulosa, seem to be capable of proliferation in vitro. The ovocytes may *divide and proliferate.* Exposure of ova to changes in temperature, hypertonic or hypotonic solutions, as well as insemination even with foreign spermia, leads to precleavage activity in the egg nucleus, extrusion of a polar body and formation of pronuclei (*Pincus,* 1940). As a rule, immature (especially embryonic) gonads grow better in vitro than adult ovarian tissue. Even human embryonic ovaries can grow in vitro to some extent

ORGAN CULTURES of cat ovaries have *been successful* using the Carrel-Lindbergh technic. At the end of several *days, the ova in their different stages* of maturation were well-preserved and the corpus luteum tissue, as well as

other cellular elements, appeared normal and indistinguishable from control ovaries fixed immediately after their removal from the body.

It is especially noteworthy that frozen, human ovarian tissue can be preserved in vitro for several days in a viable condition. Tissue cultures prepared from such material grew successfully after preservation at −12°C (*Zondek and Wolff*, 1924). Because of its possible practical applicability, this discovery stimulated a good deal of research concerning the *optimum temperature* for the preservation of ovarian tissue in vitro. Most of the relevant work was performed on guinea pig ovaries, whose viability was checked by subsequent transplantation into spayed female or intact male guinea pigs. Successful grafts were readily detected by their "feminizing" effect (nipple growth, lactation) and by the histologic structure of the transplants. At the optimum temperature (just a few *degrees above the freezing point*) guinea pig ovaries may be preserved in a viable condition in vitro for more than two weeks (*Lipschutz*, 1927-1932).

The ovary never took when preserved at temperatures beneath 0°C

Partial *drying* of the ovary, sufficient to cause a 35-57% loss of weight during preservation in vitro, does not interfere with its survival and taking, as shown by similar experiments on *the guinea pig*.

As regards the *metabolism of ovarian tissue* in vitro, it is noteworthy that a slight oxygen consumption continues for several days, even at temperatures below +1°C The metabolism of the rat ovary rises during estrus and falls during the diestrus period Furthermore, the ovaries of immature rats have a lower metabolism in vitro than those of adults

TRANSPLANTATION OF THE OVARIES

Several investigators claim to have performed successful heterotransplantations of ovarian tissue, at least among *closely-related species*. Thus, following transplantation of mouse ovaries into the ovarian capsule of rats, the subsequently discharged mouse ova can allegedly be fertilized and give rise to normal gestations in the uterus of the host rat. This claim requires further confirmation. It is undoubtedly true, however, that fertilized ova may be removed from the uterus and successfully transplanted into the uterus or even the peritoneum of other animals of the same species.

As with other endocrine glands, autoplastic transplantation of the ovaries has the greatest chance of survival, homotransplants are somewhat less likely to be successful, while heterotransplants take only in very exceptional instances (if ever) because of the incompatibility of the tissue proteins of different species

In women, autotransplants of ovaries (removed because of tumors, inflammations or other diseases in their vicinity) have frequently been successful, even pregnancies have been reported following ovarian autotransplantations into the Fallopian tubes Nevertheless the likelihood of a successful ovarian graft is much smaller in man than in most laboratory animals. Since we now possess *highly effective hormone preparations to compensate* for the loss of endocrine activity after castration, the operation is rarely justified, except for the preservation of fertility.

In the presence of adequate ovarian or testicular tissue, ovarian grafts do not tend to develop well. The results are better after unilateral and best after bilateral OVARIECTOMY or TESTIS EXTIRPATION In the body of the female castrate, corpus luteum formation, while in that of the male castrate, follicle maturation prevails, presumably because the male pituitary produces predominently FSH, that of the female LH

Intrasplenic transplants of ovaries in spayed animals often develop into folliculomas or luteomas. This is probably due to the fact that the hypophysis is freed of ovarian control when the ovarian hormones are first forced to traverse the liver, in which *they are* detoxified. Excessive luteinization of such grafts is readily accomplished by folliculoids. Progesterone or desoxycorticosterone treatment prevents this *luteinization* (see p. 417)

In HYPOPHYSECTOMIZED animals, ovarian grafts rarely take unless exogenous gonadotrophins are administered. *All*

these observations are consonant with the view that in grafts — as in the normal condition — the development of ovarian tissue is dependent mainly upon *hypophysoid trophic hormones*, and comparatively independent of nervous stimuli, which are, of course, eliminated in the transplants.

PARABIOTIC union of a castrate bearing an ovarian transplant with a castrate male or female partner causes excessive stimulation of the grafted ovary, due to the increased gonadotrophic hormone production of the hypophysis in the gonadectomized twin. In this respect again, the graft reacts like the normal ovary in similar parabiotic pairs.

TECHNIC OF OVARIECTOMY

In FISH, the usual procedure is to make a midline incision, using clean (but *not necessarily sterile*) *instruments*. The ovaries may then be removed by blunt dissection or by thermocautery. The operation has a comparatively high mortality.

In AMPHIBIA and most REPTILES the procedure is approximately the same as in fish, but it must be kept in mind that in toads, *Bidder's organ* (*see* . Comparative Morphology) undergoes compensatory hypertrophy following ovariectomy and this may interfere with the development of typical castration changes.

In BIRDS, removal of the well-developed left ovary is comparatively simple After *plucking the feathers, an incision* is made between two ribs in the ovarian region and a self-retaining retractor is inserted into the wound, so as to spread the ribs as far as possible. The air sacs, which tend to interfere, may either be pushed aside or transected. After this, all the ovarian tissue is removed, tearing the *hilum between two forceps.* Vessel ligatures are rarely necessary, except during the egg-laying period, when the vascularity of the organ is excessive. Two stitches put through skin aud muscle layers suffice to close the wound. In very young chicks, we found *it useful to remove the ovarian tissue by means of suction applied* through a fine glass cannula.

It is somewhat more difficult to remove the right ovary which is vestigial in most birds. However, if the left ovary had previously been removed, the right gonad becomes more conspicuous.

In most LABORATORY MAMMALS (cat, dog, rabbit, rat, mouse, etc.) ovariectomy is a very simple procedure. It may be performed from a single suprapubic incision, pulling the ovaries into the operative field by traction on the *uterine horns and oviducts. Some prefer* two separate costo-lumbar incisions. For most purposes (especially for bioassays in rodents) it is best to remove the ovary together with the ovarian pouch and part of the oviduct in *order to ensure that no remnants are* left behind.

In MAN, ovariectomy at any age is also simple as long as the gonad is not tumorous or adherent to its surroundings In typical cases, the usual procedure is to open the abdomen through a *suprapubic, midline incision, after* the customary preparation for abdominal operations The gonad is seized with Allis clamps and 2-3 ligatures are placed through the pedicle; after this the hilum is severed and the wound carefully peritonized, in order to prevent the formation of adhesions

Cystic ovaries may have to be punctured before they can be delivered through the abdominal incision, but care *must be taken not to spread the cyst* fluid into the peritoneum, especially if there is suspicion of infection or malignant transformation of the cyst. In many cases (e.g , malignancy) the technic of choice is HYSTERO-OVARIECTOMY.

VAGINAL OVARIECTOMY is rarely performed, although certain cysts and abscesses may become so solidly adherent

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at the time of ovariectomy, the more striking are the resulting somatic and psychic changes. *In ovariectomized* prepubertal children, the entire development of the sex organs (breasts, uterus, pubic hair, etc.) is severely inhibited, but after puberty the involution caused by spaying is less striking, and in postmenopausal women ovariectomy often fails to exert any detectable effect. Usually, though not always, women gonadectomized during adult life tend to develop excessive adiposity; in many patients this is merely due to the psychosomatic effect of castration on appetite.

Folliculoids rarely produce any pronounced signs of acute overdosage *and even excessive amounts* are comparatively well tolerated. On the other hand, adrenal deficiency, hypopituitarism or extensive destruction of the liver sensitize to the toxic effects of folliculoids, apparently because the anterior-lobe and the adrenal cortex play an important part in adaptive defence reactions against folliculoids, while the liver is the chief site of their detoxification.

In premature infants, treatment with folliculoids is claimed to exert a beneficial effect *upon development in general*. It has also been claimed that resistance to certain infections and intoxications can be altered (increased or decreased, depending upon conditions) by ovarian hormones.

There is some evidence indicating that folliculoids stimulate plant growth

Luteoids are not known to exert any characteristic effects upon the general condition *of* animals or man. Even in the largest doses so far administered, they failed to cause toxic overdosage phenomena, they may, however, produce anesthesia.

Temperature. — Neither ovariectomy nor treatment with ovarian hormones induce significant changes in body temperature The skin temperature may be slightly raised by the vasodilator effect of folliculoids and during *menopausal flushes. It is very probable* that the characteristic mild variations in body temperature during the men*strual cycle, are likewise conditioned* by ovarian hormones.

Tissue Metabolism. — The metab*olism of the accessory sex organs*, which are normally stimulated by folliculoids, is directly increased by these hormones *in vitro* (e.g., uterus, vagina). The effect of folliculoids upon the metabolism of other tissues is not conspicuous outside the body.

Basal Metabolism. — Ovariectomy often causes a slight decrease in the B.M.R. while folliculoids tend to raise it.

Carbohydrate Metabolism. — In women ovariectomy or treatment with luteoids causes no prominent changes in carbohydrate metabolism. On the other hand, folliculoids may elicit severe diabetes in animals (e.g., rat), particularly after sensitization by partial pancreatectomy and forced feeding with a high carbohydrate *diet*. This diabetogenic effect is not entirely mediated by the adrenals since, to some *extent, it is still demonstrable after* adrenalectomy

The accumulation of glycogen in the endometrium during the luteal phase is the direct effect of progesterone action. Conversely, the lining cells of the vaginal epithelium, which are free of glycogen in postmenopausal and castrate women, accumulate this carbohydrate under the influence of folliculoids.

Lipid Metabolism. — The ovary exerts no very prominent and characteristic effects upon lipid metabolism, although fat deposition is often increased in ovariectomized women. In birds, treatment with folliculoids causes very marked lipemia and cholesterolemia, presumably because the ovarian hormones play an important part in the

to the vaginal wall that an extraperitoneal, trans-vaginal approach may be advantageous.

PARTIAL OVARIECTOMY may take the form of mere excision or ignipuncture of medium-sized surface cysts, complete decortication of the ovary, or removal of the major part of its substance by wedge excision.

Under modern surgical conditions, ovariectomy in itself is not a dangerous operation and the wound usually heals by first intention without complications.

Instead of surgical ovariectomy, X-RAY CASTRATION is sometimes the method of choice, as in the treatment of certain inoperable ovarian tumors, the production of an artificial (permanent or temporary) menopause, etc

It will be seen from the section devoted to the various ovarian diseases that temporary sterilization due to X-ray amenorrhea has been recommended in functional uterine hemorrhages, endometriosis, inflammations of the ovary and diseases in which pregnancy would be dangerous. The details of ovarian irradiation as practised today have been summarized in the following table (*Schmitz*, 1944):

Roentgen Doses in r Units for the Production of Permanent and Temporary Amenorrhea Measured at the Ovary

(Factors of Production 195 KV., 0 5 mm Cu+1 0 mm Al filter, 50 cm F.S D)

AGE GROUP	Permanent amenorrhea				Temporary amenorrhea			
	Me	My-a	My-b	My-c	Me	My-a	My-b	My-c
A — 20 to 25 yr	321	324	373	462	276	277	316	400
B — 26 to 30 yr	308	311	358	444	263	266	302	382
C — 31 to 35 yr	289	298	342	424	250	254	289	362
D — 36 to 40 yr	282	284	327	398	239	242	277	342
E — 41 to 45 yr	269	271	310	379	226	230	261	324
F — 46 to 50 yr	254	256	295	360	213	218	248	307
G — 51 to 55 yr	241	243	279	341	200	207	236	290
H — 56 and over	226	230	264	321	189	195	224	272

Me = Hemorrhagic metropathy or myopathy
My-a = Myoma reaching to symphysis pubis
My-b = Myoma reaching midway between symphysis and umbilicus
My-c = Myoma extending above umbilicus

Among the dangerous *complications of X-ray castration* (due mainly to faulty technic or individual variations in X-ray sensitivity) are: damage to the skin, unintentional production of permanent amenorrhea, and the danger of causing mutations and deformities in the offspring following temporary castration.

It is presumed, though not definitely proven, that while large doses of X-rays destroy, small doses stimulate ovarian function

EFFECTS OF OVARIECTOMY AND TREATMENT WITH OVARIAN HORMONES

State — The main effects of OVARIECTOMY are the typical manifestations of hypogonadism, and so-called "menopausal disturbances" (see: Diseases of the Ovary) In general it may be said that the younger the individual

Growth and Bone Structure. — Prepubertal ovariectomy tends to increase somatic growth and to delay the ossification of junction cartilages. On the other hand, folliculoids (but not luteoids) inhibit growth in length and cause premature ossification of the epiphyses. In the case of chronic treatment with folliculoids, the proliferation of bone tissue may cause a severe reduction of the marrow spaces, conducive to anemia. This effect is particularly marked in birds, but also clearly demonstrable in mammals.

It is presumably a direct action since in ducks local bone proliferation was noted after injection of folliculoids into bones.

In addition to the above-mentioned actions on the entire skeleton, *folliculoids also exert* a specific effect upon the pubic bones. Simultaneously with the relaxation of the pelvic ligaments induced by these hormones, the adjacent parts of the pubic bones undergo absorption. Certain corpus luteum extracts (containing "relaxin") are especially active in this respect The underlying process is probably essentially analogous to the physiologic pre-

high doses of folliculoids causes severe, sometimes fatal, anemia. The pathogenesis of this change is not clearly understood. It cannot be entirely ascribed to obliteration of bone marrow cavities by proliferating bone tissue, since it is not necessarily accompanied by excessive osteosclerosis. In birds and some rodents where such obliteration is especially prominent, this in itself largely accounts for the resulting aplastic anemia.

BLOOD COAGULATION is slightly delayed following ovariectomy in most species, and the platelet count tends to decrease, but these actions are inconstant.

Cardiovascular System. — The BLOOD PRESSURE is likewise not significantly altered by ovariectomy or by ovarian hormone administration The claim that *folliculoids* increase the blood pressure in the rat has not been substantiated. Indeed, women with menopausal hypertension often show a decrease in blood pressure following folliculoid hormone therapy, although this effect is less marked than the beneficial action upon the flushes

Folliculoids exert a vasodilator effect which is readily verified by direct inspection (e.g., in the rabbit ear), or by the resulting increase in organ volume (e.g., finger volume in women). The vessels of the nasal mucosa, and those of the accessory sex organs controlled by folliculoids, appear to be especially sensitive to this effect. The innervation of the blood vessels does not appear to play an important rôle, at least as regards the vasodilatation in accessory sex organs, since this effect persists in transplants of uterine tissue. It has been assumed that the action is due to a peripheral acetylcholine discharge caused by folliculoids. Encouraging results have also been reported after folliculoid therapy in: acrocyanosis, angina pectoris, diabetic gangrene and endarteritis obliterans; but in these conditions the value of this treatment is still controversial

Luteoids do not appear to share with desoxycorticosterone the ability to *raise the blood pressure. Under certain* conditions they are even claimed to *diminish the high blood pressure of* animals with experimental renal hypertension

The HEART action is not significantly influenced by ovarian hormones although in certain cases the allegedly typical electrocardiogram of hypoovarian women and the cardiac manifestations of hyperthyroidism have been claimed to respond favorably to folliculoids.

Lymphatic System. — Ovariectomy tends to enhance, while treatment with folliculoids markedly depresses the development of the thymus; the spleen,

formation of the large lipid-containing egg-yolk.

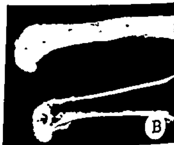
Nitrogen Metabolism.— The metabolism of protein and other nitrogenous products is not characteristically influenced by ovariectomy or the administration of ovarian hormones.

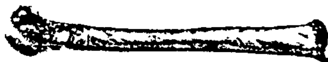
Water and Salt Metabolism. — Ovariectomy causes no very typical change in water and salt metabolism. It has been claimed that folliculoids decrease the URINE OUTPUT, but this effect is rather inconstant. In high doses progesterone exerts a marked diuretic effect in the rat and under certain conditions occasionally also in women with premenstrual edema.

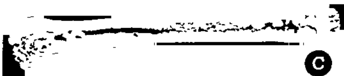
The BLOOD CALCIUM concentration is markedly increased by folliculoids in birds (probably related to egg-shell formation). In mammals this effect is extremely slight (see also: Effect of Folliculoids on Bone Formation).

It has been claimed that both folliculoids and luteoids decrease Na and Cl excretion, but this has not been confirmed. The blood chloride concentration, however, increases slightly following folliculoid treatment in most animal species, as well as in man.









Effect of folliculoids upon the bones. — A. Section through the femur of a mouse given 250γ of estradiol benzoate during 41 days. A large part of the distal marrow has been replaced by bone; the epiphyseal cartilage is thin due to reduction of both the proliferating and hypertrophic layers. — B. Ground section through the femur of a control (bottom) and folliculoid-treated mouse showing the extent of endosteal ossification. — C. and D. Long bones from an untreated (top) and folliculoid-treated pigeon showing marked endosteal bone proliferation. Similar bone deposition occurs normally during the egg-laying period.

(Courtesy of Dr W U Gardner)

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It is presumably a direct action since in ducks local bone proliferation was noted after injection of folliculoids into bones.

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Blood. — In certain species, especially in the dog, chronic treatment with high doses of folliculoids causes severe, sometimes fatal, anemia. The pathogenesis of this change is not clearly understood. It cannot be entirely ascribed *to obliteration of bone marrow cavities* by proliferating bone tissue, since it is not necessarily accompanied by excessive osteosclerosis. In birds and some rodents where such obliteration is especially prominent, this in itself largely accounts for the resulting aplastic anemia.

Blood coagulation is slightly delayed following ovariectomy in most species, and the platelet count tends to decrease, but these actions are inconstant.

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Lymphatic System. — Ovariectomy tends to enhance, while treatment with folliculoids markedly depresses the development of the thymus; the spleen,

bone marrow, lymph nodes and other lymphatic accumulations respond similarly though less markedly. Luteoids are almost inactive in this respect.

Muscles. — Ovariectomy diminishes, while folliculoids increase the spontaneous muscular activity of certain animals, especially the rat. This is reminiscent of the increased spontaneous muscular activity during estrus.

Nervous System. — Ovariectomy sometimes, but not always, causes disappearance of LIBIDO in women and this may be restored by folliculoids. In certain animals (e g., rat), normal females exhibit both feminine (sexual receptivity) and masculine (clasping reflex, pelvic thrusts, etc.) sexual patterns, and ovariectomy abolishes only the former. Injection of folliculoids and luteoids in such cases restores the female sexual behavior without influencing the male pattern. Injection of folliculoids into fowl eggs during the period of incubation leads to the development of intersexual males, whose reactions may vary between perfect masculine behavior patterns to neutral (inactive) behavior. Even chicks, in which folliculoid treatment was started as late as the 15th day of life, come to resemble sexually-receptive hens, in that they squat for treading males after 3 weeks of treatment.

The normally very stable social position of hens in the "peck-order" (the right to peck others without being pecked in return) of a flock tends to fall after folliculoid treatment The ovariectomized chimpanzee on the other hand (unless treated with folliculoids) is apparently considered "socially inferior" by intact females, as judged by her low priority rating in obtaining bananas available in a common cage Many other observations indicate that folliculoids are a social asset among the primates.

In most species, treatment with folliculoids evokes the typical female mating behavior and tends to inhibit the maternal instinct. In some animals (e.g., guinea pig) simultaneous or consecutive administration of progesterone greatly enhances this effect. In males, however, folliculoids decrease the normal sexual drive and may even induce homosexual female behavior.

The complex hormonal regulation of sexual drive is very incompletely understood as yet. Depending upon the species examined, and the dosages used, progesterone can even decrease and testosterone increase the female type of sexual behavior induced by folliculoids. Clinical experience indicates however, that in man, folliculoids tend to increase the normal libido in the female and to decrease it in the male

When given in very large doses, progesterone causes ANESTHESIA in various experimental animals. Folliculoids are very much less active in this respect. (See . The Steroids)

Certain analeptic drugs (e g., metrazol) are capable of awakening rats from progesterone anesthesia and conversely, the convulsions induced by the analeptic drugs are counteracted by luteoids. The well-known lassitude and somnolence of pregnant women could be, perhaps partly, due to excessively produced progesterone or its derivatives.

Digestive System. — The epithelium of the ORAL CAVITY tends to become atrophic following ovariectomy, and this change is corrected by folliculoid administration. (See · Menopause.)

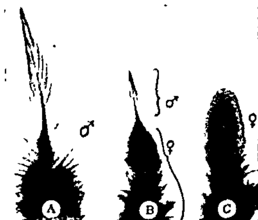
Neither ovariectomy nor treatment with ovarian hormones causes any consistently significant change in the morphologic structure, contractility and secretion of the INTESTINAL TRACT.

Degenerative changes in the LIVER, sometimes accompanied by necroses and jaundice, are produced by heavy overdosage with folliculoids in some ani-

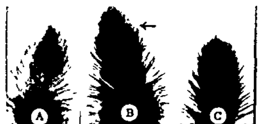
mals (e g., certain strains of mice and rats) but hardly ever in man. This may be related to the hepatic detoxification of folliculoids. Luteoids exert no similar effect.

Skin. — Under the influence of folliculoids, the SEBACEOUS GLANDS of the skin involute. This may be responsible for the beneficial action of these hormones in acne. Curiously, in some women with secondary amenorrhea, acne may develop during folliculoid therapy if they previously suffered from this skin lesion at the time of menstruation. Folliculoids also tend to cause proliferation and increased keratinization of the dermal SURFACE EPITHELIUM. These effects, as well as a certain degree of local HYPEREMIA, can also be elicited by topical application of folliculoids to certain skin regions In some animals (e g, rat) there is severe loss of hair following chronic folliculoid hormone overdosage. In hirsute women, however, this depilatory action is rarely noticeable

In certain strains of hairless mice GENERALIZED SKIN EDEMA ensues if folliculoids are given, while in most birds under the influence of such treatment, the PLUMAGE of male or gonadectomized animals becomes "hen-feathered."



Effect of ovary upon plumage. — A. Saddle hackle of spayed female silver dorking ("male type") — B. Saddle hackle growing at time of ovarian regeneration Lower part of female, upper of male type — C. Saddle hackle growing after ovarian regeneration has occurred The entire feather is of "female" type



Effect of ovariectomy upon plumage. — A. Breast feather of normal brown leghorn pullet. The feather is brown — B. Similar feather in which the part below the arrow grew after ovariectomy, this part is black. — C. Feather entirely grown after ovariectomy. The whole feather is black.





Fig. [illegible] treated with 200 mg. [illegible] of the skin not only [illegible] ompanied by marked [illegible] 5-200 mg of diethylstilbestrol/day and receiving a total of 38 gm (!) during a period of one year. Note that under the influence of continued treatment with this folliculoid the swelling of the sex-skin region was not maintained and the skin on the back and thighs returned approximately to normal. Even these huge amounts of folliculoid caused no neoplasia or anemia in this species.

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Muscles. — Ovariectomy diminishes, while folliculoids increase the spontaneous muscular activity of certain animals, especially the rat. This is reminiscent of the increased spontaneous muscular activity during estrus.

Nervous System. — Ovariectomy sometimes, but not always, causes disappearance of LIBIDO in women and this may be restored by folliculoids. In certain animals (e.g., rat), normal females exhibit both feminine (sexual receptivity) and masculine (clasping reflex, pelvic thrusts, etc.) sexual patterns, and ovariectomy abolishes only the former. Injection of folliculoids and luteoids in such cases restores the female sexual behavior without influencing the male pattern. Injection of folliculoids into fowl eggs during the period of incubation leads to the development of intersexual males, whose reactions may vary between perfect masculine behavior patterns to neutral (inactive) behavior. Even chicks, in which folliculoid treatment was started as late as the 15th day of life, come to resemble sexually-receptive hens, in that they squat for treading males after 3 weeks of treatment.

The normally very stable social position of hens in the "peck-order" (the right to peck others without being pecked in return) of a flock tends to fall after folliculoid treatment The ovariectomized chimpanzee on the other hand (unless treated with folliculoids) is apparently considered "socially inferior" by intact females, as judged by her low priority rating in obtaining bananas available in a common cage. Many other observations indicate that folliculoids are a social asset among the primates

In most species, treatment with folliculoids evokes the typical female mating behavior and tends to inhibit the maternal instinct. In some animals (e.g., guinea pig) simultaneous or consecutive administration of progesterone greatly enhances this effect. In males, however, folliculoids decrease the normal sexual drive and may even induce homosexual female behavior.

The complex hormonal regulation of sexual drive is very incompletely understood as yet. Depending upon the species examined, and the dosages used, progesterone can even decrease and testosterone increase the female type of sexual behavior induced by folliculoids. Clinical experience indicates however, that in man, folliculoids tend to increase the normal libido in the female and to decrease it in the male

When given in very large doses, progesterone causes ANESTHESIA in various experimental animals. Folliculoids are very much less active in this respect (See : The Steroids.)

Certain analeptic drugs (e g , metrazol) are capable of awakening rats from progesterone anesthesia and conversely, the convulsions induced by the analeptic drugs are counteracted by luteoids. The well-known lassitude and somnolence of pregnant women could be, perhaps partly, due to excessively produced progesterone or its derivatives.

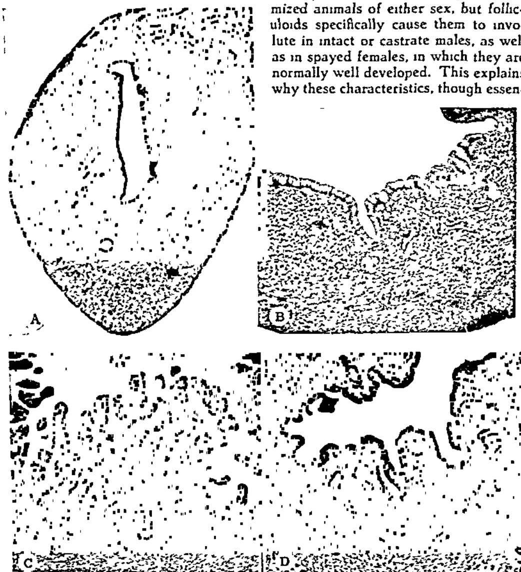
Digestive System. — The epithelium of the ORAL CAVITY tends to become atrophic following ovariectomy, and this change is corrected by folliculoid administration. (See : Menopause.)

In certain species (especially the mouse) folliculoids cause atrophy of the tubular portions in the SALIVARY GLANDS.

Neither ovariectomy nor treatment with ovarian hormones causes any consistently significant change in the morphologic structure, contractility and secretion of the INTESTINAL TRACT.

Degenerative changes in the LIVER, sometimes accompanied by necroses and jaundice, are produced by heavy overdosage with folliculoids in some ani-

tral characteristics. They do not disappear after castration in the male and appear following ovariectomy in hens. Testoids have no effect upon their development in intact or gonadectomized animals of either sex, but folliculoids specifically cause them to involute in intact or castrate males, as well as in spayed females, in which they are normally well developed. This explains why these characteristics, though essen-



Effect of various hormones upon the uterus of the spayed female rat. — A. Cross-section through the uterus, of an adult ovariectomized control rat. Note pronounced atrophy of the epithelium, thin uterine wall and narrow lumen (Same low magnification as figure B, C and

y ten days

lumen (so

scular layer

appear as

ume a high-

cylindric form — C. Uterus of an adult spayed female rat in which progestational changes have been elicited by treatment during ten days with 15 mg./day of progesterone. Note hyper-

tosterone Note that this testoid induced changes very similar to those obtainable by progesterone.

During estrus the "SEX SKIN" in the genital region of certain primates (e.g., maccaca mulatta) becomes hyperemic, the derma undergoes gelatinous transformation and the epithelium thickens. Ovariectomy abolishes this cyclic skin-transformation, while folliculoids elicit it at any time, even in the spayed female or male. Following prolonged folliculoid treatment (weeks) this skin edema tends to become generalized involving most of the body surface, but after still longer treatment (months) it disappears in spite of continued hormone administration. Luteoids inhibit the sex-skin swelling elicited by normal estrus or by folliculoids.

The PIGMENTATION of the skin especially around the nipples is increased by folliculoids in women as well as in certain animals (e.g., guinea pig). This may have something to do with the "chloasma uterinum" characteristic of pregnancy and some ovarian dysfunctions.

It is questionable whether the induction of NUPTIAL-COLORING in the skin of lower vertebrates, especially fish (e.g., bitterling) is specifically due to folliculoids, since many other compounds have similar effects.

Urinary System. — Neither ovariectomy nor ovarian hormones exert important actions upon the KIDNEY, though folliculoids tend to cause atrophy of the renal tubules, sometimes accompanied by degenerative changes. Sometimes there are also extensive hematogenous (yellowish-green) pigment-deposits in the convoluted tubules. These presumably result from the erythrocyte destruction occasioned by marked hyperfolliculoidism. They are especially prominent, and accompanied by generalized icterus, in rats receiving thyroxine and folliculoids simultaneously. In certain species (e.g., mouse) there is also distention of the ureters, hypertrophy of the walls of the ureters, bladder and urethra; and sometimes metaplasia of the bladder epithelium or formation c urinary calculi.

Accessory Sex Organs. — We de signate as "accessory sex organs," c sex characteristics, those structure other than the gonads which are char acteristic of one sex. These may b subdivided into: (1) female, (2) mal (3) neutral and (4) bisexual sex char acteristics.

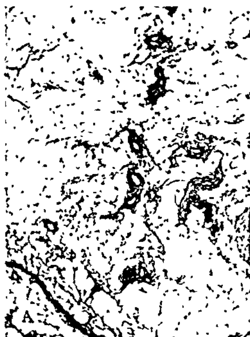
In general, the female accessory se characteristics are stimulated by ova rian hormones, and their physiolog development is inhibited by ovariec tomy. The male accessory sex char acteristics are dependent upon testoids and their normal development is impeded by orchidectomy. Neutral characteristics may occur in either sex, but their development is only inhibited by the hormones of the sex in which they are normally absent. Probably "neutral" sex characteristics are independent of the gonads and the hormones of the sex in which they are normally absent merely inhibit their development. Bisexual characteristics are identical manifestations of male and female sex hormones.

This somewhat complex problem may best be illustrated by the example of the FOWL, in which all four types of accessory sex characteristics are clearly distinguishable.

A typical *female* accessory sex organ of the fowl is the oviduct, which is well-developed in the sexually mature female, regresses after ovariectomy and is restored by folliculoid hormone administration.

Typical *male* sex characteristics are the comb, wattles, ear lobes, and the characteristic fighting instinct of the cock. They are well-developed in the sexually mature males, vanish following castration and are restored by testoids, but not by luteoids or folliculoids.

The spurs and the brilliant long feathers (especially the tail feathers) so typical of the male, are actually *neu-*



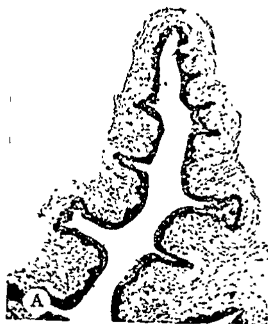


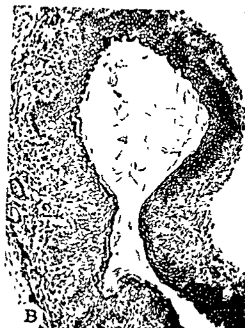




. Mammary
discernible
gland of an
adult female rat, following 10 days treatment with 5 γ/day of ethynyl-estradiol Note great

mammary development Both ducts and acini are stimulated, though not as markedly as with folliculoids or luteoids









Effect of various hormones upon the vagina of the spayed female rat. — A. Vagina of a spayed *female control rat* Note severe atrophy of the epithelium which consists of two layers of cells only The basal layer is the matrix the inner
type (Same magnification as fig B, C and D) — B.
estrus has been induced by treatment during ten days w
stratification of the epithelium with cornification of the
are shed off into the lumen — C. Vagina of a spayed adult rat after 10 days treatment with 15 mg /day of progesterone Note stratification of the epithelium with pronounced mucification (white cells) of the inner layers Similar changes can be produced with much smaller doses of progesterone in animals previously sensitized with folliculoids, but the experiment indicates that pr
— D.
testoste
intra-ep

cularly well-developed in rodents (e.g., mouse, rat) of either sex although they are *normally* larger in the male. They show but little atrophy following ovariectomy and are not significantly stimulated by folliculoids. Luteoids cause some increase in their size and secretion, but as in the case of the clitoris itself, these glands are mainly responsive to testoids. Crude anterior-lobe extracts enhance this effect of the testoids.

Bartholin's glands involute after ovariectomy and are selectively stimulated by folliculoids.

The *mammary glands* involute following ovariectomy and undergo proliferative changes (with little, if any, secretion) under the influence of folliculoid or luteoid hormones. This proliferation is most pronounced with mixtures of folliculoids and luteoids. Hypophysectomy *almost completely prevents* this effect and hence, it is probable that the mammary stimulation by ovarian hormones is predominantly mediated by the mammogenic principle of the anterior-lobe. Withdrawal of ovarian hormone treatment is usually followed by a transitory period of lactation

In lactating animals and women large doses of folliculoids (but not luteoids) inhibit lactation. Advantage is taken of this in women when lactation is not desirable (stillbirth, abortion, mammary diseases, *contagious diseases*, etc.). Painful engorgement of the lactating, unemptied breast can be minimized in these patients by transitory treatment with high doses of folliculoids. Judged by experiments on the rat, combined treatment with folliculoids and luteoids exerts an even greater antilactation effect and folliculoids inhibit lactation more actively in intact (corpus luteum bearing) than in spayed rats Very small doses of folliculoids actually stimulate milk secretion (e g , goat).

All the *male accessory sex organs* undergo atrophy under the influence of *folliculoids in intact animals and man* This is due to the resulting Leydig cell atrophy and not to a direct action on the peripheral target organs. In castrate males, whether the accessory sex organs are atrophic or well-developed due to testoid administration, folliculoids cause no inhibition. However, the folliculoids do exert a specific, direct stimulating effect upon certain male accessory sex organs. Thus either in intact or in castrate males (especially in rodents) they induce keratinization of the normally not-keratinized epithelium in the seminal vesicles and to a lesser extent, even in the prostate and the "utriculus prostaticus" (a "female" Mullerian vestige in the prostate). Simultaneously, there is marked proliferation of the fibrous and muscular *tissue in the walls of the seminal vesicles* (to a lesser extent in the prostate). The proliferation of these mesenchymal structures in the seminal vesicle walls has often been misinterpreted as a testoid effect, hence, it is well to keep in mind that not every increase in the weight of the *seminal vesicles* is necessarily indicative of the so-called "androgenic" stimulation.

Sexual Cycle. — The sexual cycle is interrupted by ovariectomy, folliculoids, or luteoids. Ovariectomy causes continuous anestrus in animals, and amenorrhea in women, because of the resulting sex-hormone deficiency. Extensive partial ovariectomies on the other hand, tend to cause continuous estrous changes due to the formation of persistent follicle cysts (see also page 376).

Folliculoids, if given in sufficiently high doses, interrupt the sexual cycle, because they cause ovarian atrophy and a continuously "follicular phase" endometrium (often metropathia hemorrhagica in women) or (at least in rodents) in high doses they prolong the life-

tially neutral, are physiologically nonetheless characteristic of male birds.

The paucity of fat deposits is a *bisexual* characteristic since the adiposity of male or female castrates can be corrected by sex hormones of either sex.

The above statements hold for instance in most of the common varieties of fowl. It must be kept in mind however, that in many birds the development of the accessory sex organs follows a different pattern and their hormonal regulation, in each species, is not yet fully clarified. There are no clear-cut instances of neutral sex characteristics in man, although the elongation of the extremities in comparison with the trunk is a closely related phenomenon since it tends to occur after early gonadectomy in either sex, conversely, pubic and axillary hair growth is bisexual as it is stimulated by either type of sex-hormone.

It would hardly be profitable to discuss the hormonal regulation of the accessory sex organs in all the numerous species in which pertinent studies have been performed Hence we shall limit our remarks to the most important laboratory MAMMALS and to man

The *oviduct* involutes and its contractility diminishes following ovariectomy. Conversely, treatment with folliculoids stimulates its development in immature or castrate females. This effect is dependent upon an adequate supply of folic acid, especially in birds. Folliculoids also cause mitotic division and secretion of the lining epithelium and they enhance the motility of the oviduct musculature, thus promoting the passage of ova. Luteoids on the other hand, inhibit the motility of the oviduct in animals as well as in women.

The *uterus* involutes after ovariectomy. Folliculoids increase uterine size (myometrium and endometrium) and induce the so-called "follicular phase or "estrous type" of endometrial change, while luteoids (especially if administered following pretreatment with folliculoids) cause progestational transformation, that is, the "luteal phase" type of mucosa. The histologic character of these changes is different in the various species but essentially, the folliculoids imitate the uterine changes of the preovulatory, and luteoids those of the postovulatory part of the sexual cycle.

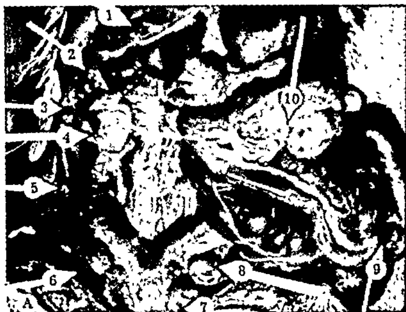
In several animal species the motility of the uterus in vitro is increased by folliculoids and diminished by luteoids, in fact the latter can even counteract the oxytocic action of posterior-lobe hormones. However, in women the amplitude of the individual spontaneous uterine contractions and sensitivity to oxytocin actually increase under the influence of progesterone.

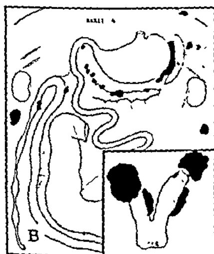
Chronic overdosage with folliculoids causes squamous metaplasia of the normally cylindric endometrial epithelium, especially in the rat. Traumatization of the endometrium elicits "endometrial moles" in folliculoid, and "deciduomas" in luteoid hormone, pretreated animals (see · Tumorigenesis, below).

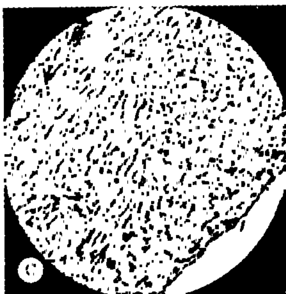
The *vagina* responds essentially in the same manner as the uterus, inasmuch as it undergoes atrophy following ovariectomy, and estrous changes under the influence of folliculoids, while luteoids reproduce the vaginal changes normally seen during the luteal phase of the sexual cycle. (See : Sexual Cycle.)

The *clitoris* undergoes no great variations in its development, either following ovariectomy or under the influence of folliculoid and luteoid hormones. It appears to be a vestigial "male" organ, responsive mainly to testoids, which in the female are predominantly of adrenal-cortical origin.

The *preputial glands*, the ducts of which open near the clitoris, are parti-









Experimental uterine fibroids. — A Uterine and extrauterine fibroids in the abdominal cavity of the guinea pig, induced by six [illegible]

epiploon, mesocolon and spleen — C. and D. Histologic structure of uterine fibroid induced in guinea-pig by three months treatment with folliculoids The tumor consists mostly of fibroblast-like, spindle-shaped cells and collagenous fibers

(Courtesy of Drs A Lipschutz R Iglesias and L Vargas)

span and activity of the corpus luteum. In either case, the cyclic occurrence of a "withdrawal bleeding" is impeded.

High doses of luteoids maintain a progestational endometrium beyond the normal span of the luteal phase and hence, they likewise prevent withdrawal bleeding at the end of each cycle. It must also be remembered that prolonged treatment with either folliculoid or luteoid hormones causes compensatory atrophy of the ovaries, a type of "functional castration." In senile or prepubertal individuals, brief treatment with folliculoids sometimes initiates a series of normal sexual cycles.

Pregnancy. — Contrary to common belief, it is extraordinarily difficult to produce abortion with folliculoids. In certain animals, exceedingly high doses have led to placental hemorrhages and abortion, but this is rather exceptional Luteoids tend to prolong gestation, allegedly because they interfere with the uterine contractions which initiate delivery; however, as previously stated, progesterone increases the contractility of the human uterus in situ so that the prolongation of gestation must be due to a different mechanism

Ovariectomy causes abortion in all animal species including man, if it is performed early enough, but the length of time during which the ovary is indispensable for the maintenance of pregnancy varies In the rat, ovariectomy causes abortion at any time during pregnancy, while in women, after the third month of gestation, removal of the ovaries rarely interferes with the subsequent course of pregnancy and delivery Apparently by that time the placenta has taken over the endocrine functions of the gonad so that the ovary becomes dispensable.

Lactation. — The influence of ovarian *hormones* upon lactation has been discussed above in connection with their other effects on the growth of mammary tissue (see: Accessory Glands on page 367).

Fertility. — Not only ovariectomy, but even overdosage with folliculoids or luteoids may cause sterility due to disturbances in the cyclic transformations of the sexual organs and the compensatory ovarian atrophy.

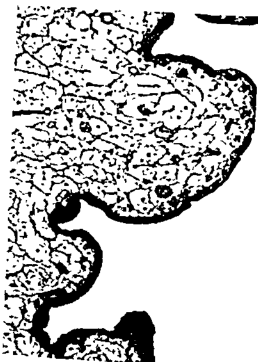
Hibernation. — There is no reason to believe that ovarian hormones exert any important influence upon hibernation. The ovarian atrophy which occurs at that time is merely secondary

Tumorigenesis. — The chemical resemblance between many of the "carcinogenic hydrocarbons" and the natural folliculoids has been emphasized in the section: The Steroids. There we also mentioned that many of these carcinogenic hydrocarbons exhibit marked folliculoid activity. We have *reason to* believe that the reverse is likewise true and that folliculoids can be carcinogenic.

It has long been known to physicians that there are close relations between ovarian function and tumor formation The great prevalence of carcinoma, especially in the accessory sex organs (uterus, mammary glands, etc.) during the climacteric age, and numerous experimental observations called attention to such interrelations.

In the UTERUS, *cancer* formation is especially frequent during the climacteric age when folliculoid hormone production, though diminished in quantity, is often more or less continuous because of the failure of corpus luteum formation In women with folliculomas, in whom there is continuous excessive folliculoid production, uterine cancers are also common. In certain strains of mice (less readily in the rat), chronic treatment with folliculoids tends to produce endometrial cancers It has not been clearly demonstrated that continuous folliculoid therapy can cause uterine carcinoma in women or in other primates (e g., monkey), but "pre-

limited life-span inasmuch as it regresses spontaneously in spite of continuous hormone treatment. It never metastasizes and is not invasive.



Experimentally-produced endometrial mole. Section through the uterus of a rat in which endometrial trauma, during the second half of gestation, produced a typical "endometrial mole." Note the epithelial lining cells and the hydropic stroma, which resembles that of the 'hydatidiform mole' of the human placenta. Essentially similar tumors can be produced by trauma in folliculoid pretreated rats. The experiment indicates that during the second half of gestation there is apparently too much folliculoid hormone in the body to permit deciduoma formation and under these conditions endometrial moles develop after trauma

Many tumors of the MAMMARY GLANDS are indubitably under ovarian hormone control. In women with mammary cancers, ovariectomy has frequently been practiced with at least temporary success. Chronic treatment with folliculoids may cause a typical proliferation of mammary tissue, but it has not yet been shown that true mammary cancers can be provoked by such therapy in women. Indeed, high doses of folliculoids, especially stilbestrol, are claimed to impede the development or cause regression of spontaneous breast cancers, particularly in elderly women; in younger women such treatment sometimes appears to cause the reverse effect.

In experimental animals, especially in certain particularly cancer-susceptible strains of mice (less readily in rats), chronic treatment with folliculoids produces mammary carcinomas or fibroadenomas. In the susceptible strains of mice, the breast cancers develop much more frequently in females than in males; they occur only some time after sexual maturity and their development is impeded by ovariectomy but enhanced by folliculoid treatment. The so-called "milk-factor" (probably a virus transmitted from the mother through the milk) predisposes the offspring to mammary cancer, and increases sensitivity to the tumorigenic



Uterine carcinoma following folliculoid treatment. Squamous carcinoma of cervix (or upper vagina) in a hybrid mouse that received 33.3 γ of estradiol benzoate weekly, for 73 weeks (Courtesy of Dr W U Gardner)

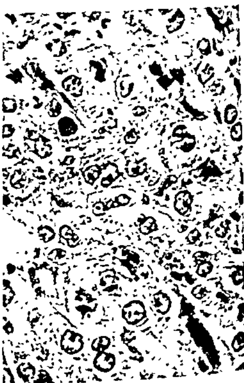
cancerous" lesions in the cervix uteri have been elicited with these hormones in maccaca mulatta. In the rat, chronic experimental hyperfolliculoidism causes keratinization of the entire endometrium

Fibromyomas are also frequent in women suffering from hyperfolliculoidism. Since these growths tend to regress after ovariectomy, it is reasonable to assume that they are, at least partly, dependent upon stimulation by ovarian hormones. In the guinea pig, uterine and even extrauterine *fibromas* (usually without myomatous elements) can be produced by folliculoids. It is interesting that their development is inhibited by progesterone, testoids, and many other steroid hormones, which are commonly referred to as "anti-fibromatogenic." The relationship between these experimental fibromas, and the spontaneous fibromyomas of women has not yet been fully elucidated.

Whether *endometriosis* should be regarded as a neoplastic disease is debatable. It is noteworthy, however, that this invasive type of endometrial growth (which may even metastasize) is extremely prevalent among women with hyperfolliculoidism, never occurs before puberty and consistently regresses during the menopause or after castration. Experimental invasive endometriosis (with uterine glands penetrating the entire wall of the uterus and emerging under the peritoneum) has been produced by chronic folliculoid hormone administration in the guinea pig and rabbit.

Uterine polyps are likewise prevalent among women with hyperfolliculoidism. they also tend to regress after the menopause and ovariectomy. In rabbits and guinea pigs, chronic folliculoid treatment has been shown to produce experimental endometrial polyps. In this connection the frequent association of uterine polyps with *metropathia hemorrhagica* is also noteworthy, since the latter is certainly due to hyperfolliculoidism.

The experimental *deciduoma* (or "placentoma") is a typical neoplastic growth elicited in the endometrium by local trauma. It can only be produced after pretreatment with luteoids, during the luteal phase of the cycle, or during pseudopregnancy, that is, in the presence of corpus luteum hormone. Here the rôle of both local trauma and ovarian hormones is manifest.



Experimental deciduoma. Numerous mitotic figures in a deciduoma which was produced in a spayed female rat, sensitized with estradiol and progesterone, prior to endometrial traumatization.

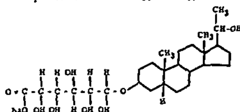
Endometrial moles are edematous, myxoma-like tumors of the endometrial stroma They greatly resemble the so-called hydatidiform moles, which develop spontaneously from placental elements in women The endometrial mole is elicited by uterine trauma in folliculoid hormone pretreated animals, especially the rat and rabbit Like the deciduoma, the endometrial mole has a

Apparently all steroid hormones, including the folliculoids and luteoids, are partly INACTIVATED in the body. Only comparatively small amounts are eliminated, through the urine or bile, in an active form. This inactivation is accomplished by: total oxidative degradation of the nucleus itself; by reduction (e g., progesterone to pregnanediol); and by conjugation. All these processes appear to depend upon the activity of certain enzymes (e g., "estrinase") present in various tissues, especially the liver.

Very little is known about the pathways through which complete OXIDATIVE DISINTEGRATION of the steroid nucleus occurs in the body. There is satisfactory evidence to show, however, that the side chain in some 17-ethyl-*androstane* (allo-pregnane) derivatives can be split off at the C_{17} carbon atom by oxidative processes.

Much more is known about the CONJUGATION of steroids. The urinary steroids possess a hydroxyl group which can be conjugated by the formation of *ethereal sulfates* or *glucuronides;* these are usually excreted in the form of their sodium salts. Estriol glucuronide, estrone sulfate, pregnanediol glucuronide, and among the testoid derivatives, androsterone sulfate and trans-dehydro-androsterone *sulfate* (the latter prepared as a semicarbazone), have actually been isolated from urine. Unlike the free steroids, the conjugates are highly water-soluble and perhaps this facilitates their elimination through the urine. Conjugation lessens the biologic activity of the steroids when they are given parenterally, but increases it in the event of administration by the oral route.

In the glucuronides of estriol and pregnanediol the hydroxyl group of the steroid combines with the aldehyde group of glucuronic acid (glucosidic linkage). Since the reducing property of the latter depends on the aldehyde group, such conjugates do not reduce alkaline copper solutions. However, following hydrolysis by boiling with dilute acids, free glucuronic acid is liberated from the conjugates and then its reducing properties (similar to those of glucose) become evident again. In pregnanediol glucuronide, the conjugation occurs at C_3, while in estriol, it takes place either at C_{16} or C_{17}.



Pregnanediol Sodium Glucuronidate

There is ample evidence to show that conjugation of steroids with either sulfuric or glucuronic acid occurs in the LIVER. Hepatectomy or liver damage by toxic substances (chloroform, carbon tetrachloride, etc.) prevents such conjugative processes.

Conversely there is evidence that certain folliculoid precursors or "profolliculoids" are activated in the body, judged by the fact that, for instance, estriol is more active in immature intact than in spayed rats. The ovary could be one such site of activation.

Occurrence of Folliculoids in Various Body Tissues and Fluids. — α-ESTRADIOL has been found to occur in various tissues such as: sow ovaries (0.014 mg./Kg.), human placenta (0.038 mg./Kg.) and horse testes (0.21 mg./Kg.). It is apparently not present in the adrenal cortex and occurs only in traces in the urine of normally cyclic or pregnant women and pregnant mares.

ESTRONE has been prepared from: sow ovaries (0.01 mg./Kg.), human placenta (0.035 mg./Kg.), horse testes (0.36 mg./Kg.), sow adrenal cortex (0.08 mg./Kg.), the urine of normally cyclic (traces) or pregnant (1 mg./L.) women and pregnant mares (100 mg./L.)

effect of folliculoids. The development of experimental fibroadenomas of the mammary gland which can be produced by folliculoids in the rat, is inhibited by simultaneous progesterone treatment.

Whether *cystic-glandular hyperplasia* of the breast should be regarded as a neoplasm is doubtful, but it probably represents a precancerous condition. It is especially common in women with hyperfolliculoidism and can be experimentally produced by folliculoids in animals (especially the mouse and rat): the spontaneous form in women tends to regress after ovariectomy.

It is doubtful whether cancer of the VAGINA is related to ovarian hormones. *Kraurosis vulvæ*, probably a precancerous lesion, is frequently ameliorated by folliculoid therapy.

In certain strains of mice, tumors (usually sarcomas) of the LYMPHATIC ORGANS, sometimes accompanied by LEUKEMIA — occur in a very high percentage of animals treated with folliculoids. In mice predisposed to the formation of spontaneous HEPATOMAS, the development of these tumors is likewise enhanced by folliculoids. It is somewhat more doubtful whether the TRANSPLANTABLE, SPONTANEOUS TUMORS of animals and those induced by CARCINOGENIC HYDROCARBONS are likewise influenced by ovarian hormones, although some investigators claim that their growth is also enhanced by folliculoids.

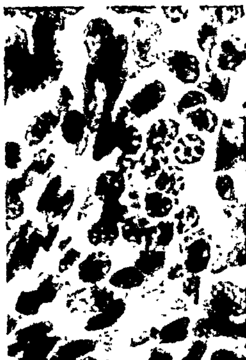
The effect of folliculoids upon tumorous growths in other endocrine glands is discussed in the sections dealing with the adrenals, the hypophysis, and the testis, respectively. In order to complete this summary, we wish to mention, however, that chronic treatment with folliculoids can lead to the development of ADRENAL-CORTICAL ADENOMAS OR CARCINOMAS and LEYDIG CELL TUMORS (especially in predisposed strains of mice), as well as chromophobe ADENOMAS OF THE ANTERIOR-LOBE (especially in the mouse and rat).

CANCER OF THE PROSTATE appears to be, at least to some extent, under the influence of testoids produced by the Leydig cells. It is for this reason that castration often causes, at least a temporary, improvement (see: Testis) in patients suffering from prostatic cancer. Treatment with folliculoids tends to cause a similar improvement, probably because of a functional castration due to Leydig-cell atrophy.

IN CONCLUSION, we may say that the evidence mentioned above clearly indicates that folliculoids can produce neoplasms, especially in the accessory sex organs, the adrenals, the testis, and the pituitary. This tumorigenic effect is frequently inhibited by simultaneous treatment with luteoids or testoids. It is less clear whether folliculoids can produce tumors in organs other than the accessory sex organs and endocrines, except in hereditarily predisposed individuals. There is some indication that in certain specific instances, folliculoids may also have an antitumorigenic effect (prostatic cancer, mammary cancer?).

METABOLISM OF THE OVARIAN HORMONES (OVARIAN HORMONE CONTENT OF BODY FLUIDS AND TISSUES)

The main problems in connection with the metabolism and biogenesis of the ovarian hormones are discussed in the section: The Steroids. The variations in the ovarian hormone content of the blood and urine have been mentioned in connection with those diseases in which they are of diagnostic importance. Additional pertinent facts will be found in the sections: Sexual Cycle and Pregnancy. Here, we shall merely give a brief outline of the main facts concerning the metabolism of the ovarian hormones.



"Wheel cells" in the ovary of the hypophysectomized rat. Note peculiar arrangement of chromatin in rounded nuclei of theca cells (center of the field), the light spaces between the chromatin granules resemble spokes in a wheel

Treatment with suitable combinations of *anterior-pituitary extracts* can restore the normal structure of the ovary in hypophysectomized animals There are great species differences in the responsiveness to this substitution therapy: primates, including man, are least amenable to such treatment. As indicated earlier (see · Theories concerning the *Hypophysoid Hormones*), there is no agreement as yet concerning the number of chemically-distinct hypophysoid gonadotrophic principles The chief factors probably responsible for the rather confused picture presented by the pertinent literature are · species differences in responsiveness, variations in the degree of purity, the dosage, or the relative proportions of the gonadotrophins administered and the timing of the injections The following is a simplified summary of the most important relevant facts (mainly gathered from experiments on rats)

(1) *FSH* causes follicle maturation *without luteinization and without any* evidence of either folliculoid or luteoid hormone secretion, as judged by the condition of the uterus and vagina.

(2) *LH* causes luteinization of the theca cells with formation of thecal corpora lutea It also restores the wheel-cells to normal, subsequently transforming them into theca-lutein cells, and expedites the involution of pre-existent corpora lutea In itself it does not cause luteinization of the granulosa LH stimulates the pre-existent theca and corpus luteum cells to form folliculoids, but elicits no luteoid hormone secretion as judged by the condition of the accessory sex organs, which show estrus but no progestation.

In prepubertally hypophysectomized animals, LH produces no estrus unless precocious puberty has been elicited by gonadotrophins prior to the hypophysectomy.

(3) *FSH plus LH* causes follicle stimulation and luteinization, especially if the FSH treatment preceded LH administration. Under optimal conditions of dosage *and timing, ovulation* may also be obtained in the hypophysectomized animal by successive treatment with *FSH* and *LH*. It is not necessary *therefore, to assume the* existence of a special "ovulation hormone" Combined treatment with *FSH and LH, causes folliculoid, but no* luteoid hormone secretion by the ovary. It expedites the involution of pre-existent corpora lutea, even more than LH treatment alone Excessive doses of FSH and LH, or combined treatment with both these substances may elicit the formation of many more follicles and corpora lutea *in the ovaries* of hypophysectomized animals than would occur, normally, in intact animals.

(4) *Luteotrophic hormone* (prolactin) exerts no significant effect upon

Estriol has only been found in human pregnancy urine (9 mg./L.) and in human placenta (0.14 mg./Kg.), while none appears to be present in pregnant mare's urine, sow's ovary, and other tissues. Perhaps this compound is produced only by the human placenta.

A number of other folliculoid compounds, e.g., equilin, equilenin, and hippulin, appear to occur only in the urine of horses, perhaps because of species-specific peculiarities of their intermediate metabolism.

The folliculoid hormone concentration in the corpus luteum is approximately the same as in ovarian follicles.

Progesterone is not found in any part of the ovary except the corpus luteum, and is not eliminated as such in the urine There is indirect evidence to show that the placenta can also produce luteoid compounds, perhaps progesterone itself.

The urinary excretion of pregnanediol sodium glucuronidate is only an approximate measure of ovarian progesterone formation, since the adrenal cortex can also produce progesterone and other steroids which are eliminated in the form of pregnanediol sodium glucuronidate. Excretion of this compound commences one or two days after ovulation and reaches a maximum about one week prior to the onset of bleeding. It disappears from the urine almost completely two to three days before menstruation It must also be remembered that progesterone can be excreted in the form of less completely reduced compounds (e.g., allo-pregnanolones) and perhaps, after oxidative degradation of the steroid ring structure, even in the form of smaller molecules. (See also pp. 80-84)

STIMULI INFLUENCING THE OVARY

Extirpation of Endocrine Glands. — Hypophysectomy causes pronounced retrogressive changes in the ovaries of all laboratory animals. In adults, follicle maturation, ovulation and corpus luteum formation cease. At the same time, all pre-existent follicles which were fairly mature at the time of the operation, undergo atresia, while the very immature, especially the primary follicles persist indefinitely in spite of the hypophyseal deficiency Indeed, even the formation of new follicles from the germinal epithelium is not abolished. The theca cells of the atretic follicles do not degenerate as completely as their granulosa cells and ova, but in several animal species (e.g., rat) they undergo a retrogressive process designated as "wheel-cell formation." During this transformation, the originally spindle-shaped theca cell becomes roundish and loses most of its cytoplasm, while the nucleus becomes similar to that of the plasma cells. The dense nuclear chromatin rearranges itself in such a manner as to leave radially oriented, clear, wheel-spoke-like spaces between the chromatin granules In some animal species (e.g., rat) the pre-existent corpora lutea involute very slowly after hypophysectomy, while in others (e.g., mouse) their disappearance is rapid.

In the ovaries of prepubertally hypophysectomized animals, pituitary deficiency manifestations are also evident. Since advanced stages of follicle maturation or corpus luteum formation do not occur in any case at such an early age, only the wheel-cell formation is very obvious However, this suffices to show that gonadotrophic stimulation is of importance for the development of ovarian structure even before the advent of puberty.

testoid hormone production is demonstrated by the subsequent masculinization of the plumage, comb, wattles and sometimes even the growth of spurs. Probably most instances of spontaneous transformation of a laying hen into a rooster with male libido and all the male accessory characteristics, are due to destruction of the left ovary by disease and subsequent development of the rudimentary right ovariotestis.

If a spayed and an intact female rat are PARABIOTICALLY UNITED, the ovaries of the normal partner increase in size due to the development of many follicles and corpora lutea. Even if both the spayed and the intact partner are prepubertal, intense luteinization occurs, indicating that precocious, excessive gonadotrophin production by the castrate continues *in spite of the ovarian enlargement* in the intact parabiotic twin. Normally, the gonadotrophin-secretion inhibiting effect of ovarian hormones keeps the anterior-lobe activity down to a physiologic limit; however, in the case of parabiosis *apparently only* the gonadotrophic, but not the ovarian hormones, pass freely across from one twin to the other. Thus, the gonadotrophic hormones of both pituitaries would act on the ovaries *of the intact partner*, but the ovarian hormones of the latter could not effectively prevent the increased function of the spayed twin's hypophysis. It is also noteworthy that this increased *ovarian stimulation may persist* for more than a year without any evidence of antihormone formation against the endogenous gonadotrophins.

Parabiotic union of an intact female with a castrate *male rat results in a* similar ovarian response, but in this case usually follicle stimulation prevails over luteinization. Apparently the male castrate tends to produce more FSH than the *spayed female*.

Removal of the OTHER ENDOCRINE GLANDS (adrenals, thymus, thyroid, parathyroids) causes no noteworthy ovarian changes beyond those explicable on the basis of the non-specific damage occasioned by such interventions.

UTERUS EXTIRPATION tends to prolong the life span of corpora lutea, *especially in the guinea pig*. It is doubtful, however, whether the involution or cystic degeneration of the ovaries often seen in hysterectomized women, is due to any deficiency in *hypothetic "uterine hormones." In most species* including man, hysterectomy usually does not interfere with the ovarian cycle and it is quite probable that most, if not all, the ovarian lesions ascribed to uterine deficiency *are actually due to incidental damage* to the blood supply of the gonad. The responsiveness of the ovary to exogenous gonadotrophins is not significantly altered by hysterectomy.

SURGICAL INTERVENTIONS ON THE NOSE AND EYES may elicit structural changes in the ovaries which have been ascribed to specific derangements in the nervous regulation of gonadotrophin secretion. (See *Effect of Rays on pp. 384, 385.*)

Hormones. — HYPOPHYSEAL EXTRACTS act somewhat differently in normal individuals from what has been said above about the response of hypophysectomized *animals. This is due to the* peculiar ability of the test-animal's own pituitary to complement the action of *exogenous hormones by endogenous* secretion of other, synergistic *hormones. Without entering into details* regarding species-specific responses, dosage, timing of the administration of certain principles, etc., the most important pertinent facts (mainly gather*ed from experiments on the rat) may* be summarized as follows:

(1) *FSH* produces predominantly follicle stimulation, but this is rapidly followed by corpus luteum formation, *presumably* due to LH *production* by the animal's own pituitary.

(2) *LH* causes predominantly corpus luteum formation, but also some

the ovary of hypophysectomized animals, unless there are functional corpora lutea at the time of operation. In this event, it maintains the corpus luteum — both morphologically and functionally — in the absence of the pituitary. It causes luteoid hormone production by the pre-existent corpus *luteum cells, as judged by the condition* of the uterus (progestation) and vagina (mucification). Indeed, the amount of luteoid hormone thus produced suffices to permit the formation of deciduomas following local trauma to the endometrium.

(5) There is no reason to believe that pure *adrenotrophic, thyrotrophic, somatotrophic*, or any of the *intermediate* and *posterior-pituitary hormones*, exert any specific effect upon the ovary of the hypophysectomized animal.

(6) None of the *steroid hormones* appear to have a direct effect upon the ovary, except the folliculoids which may slightly delay the ovarian involution following hypophysectomy in certain species. When given in combination with gonadotrophic pituitary extracts, folliculoids enlarge the size of the developing follicles and corpora lutea, so that eventually, "pregnancy type" corpora lutea develop. This is presumably due to a peripheral synergism between the action of luteotrophin and of folliculoids upon the corpus luteum.

(7) Hypophysectomy during late *pregnancy* does not cause involution of the corpora lutea. *Treatment of hypo*physectomized, pregnant animals with LH prevents the formation of wheel-cells in the theca, but results only in theca luteinization, not in follicle formation, as it would in intact animals. From this it was concluded that the placenta (though *capable of maintaining* the corpora lutea of gestation, thus substituting for the luteotrophic effect of the pituitary) does not possess the ability of the hypophysis to complement the effect of injected LH by the secretion of FSH.

(8) Hypophysectomy during *pseudopregnancy*, elicited by lactation, copulation, or mechanical stimulation of the uterine cervix, causes involution of the corpus luteum of pseudopregnancy. In such an animal as the rabbit, *in which copulation leads to* ovulation within 10 to 12 hours, hypophysectomy prevents the formation of the corpora lutea, but only if it is performed during the first hour after coitus. Later removal of the pituitary is ineffective, apparently because sufficient gonadotrophin has been secreted during the first hour to insure ovulation and corpus luteum formation.

PARTIAL OVARIECTOMY causes a compensatory hypertrophy of the remaining ovarian tissue and, as long as the *ovariectomy is not too extensive*, the remnant tends to compensate for the deficiency according to the "law of constant numbers" (see : Theories concerning the Histophysiology of the Ovary). Hence, fertility and the number of offspring per litter are not necessarily diminished by *partial ovari*ectomy. On the other hand, after very extensive partial resections, the small ovarian remnant tends to show cystic degeneration, due to excessive growth and persistence of non-ovulating mature follicles. This is accompanied by protracted estrus The uterus then often enlarges, cystic glandular hyperplasia and adenomatous polyps may be *produced. and proliferating* glands may penetrate deeply into the myometrium. This condition has been ascribed to a derangement of the hypophyseal-ovarian relationship

In birds (e g, fowl) in which only the left ovary is fully developed and capable of egg production, removal of this gonad (especially if performed at an early age) may cause transformation of the rudimentary right ovary into an "ovario-testis" containing both male and female elements Actual spermatogenesis may develop in these ovario-testes and their

testoid hormone production is demonstrated by the subsequent masculinization of the plumage, comb, wattles and sometimes even the growth of spurs. Probably most instances of spontaneous transformation of a laying hen into a rooster with male libido and all the male accessory characteristics, are due to destruction of the left ovary by disease and subsequent development of the rudimentary right ovariotestis.

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(1) *FSH* produces predominantly follicle stimulation, but this is *rapidly* followed by corpus luteum formation, presumably due to LH production by *the animal's own* pituitary.

(2) *LH* causes predominantly corpus luteum formation, but also some

follicle maturation, probably owing to the compensatory secretion of FSH by the animal's own pituitary.

(3) *FSH plus LH* causes a much more pronounced ovarian weight increase than either of these hormones alone, but the result is qualitatively similar to that produced by FSH or LH given singly. There is both follicle maturation and corpus luteum formation. While LH raises the ovarian weight only to a certain, limited extent irrespective of dosage, combined administration of FSH and LH is capable of producing a weight increase over a much greater range of dosages. Hence the most pronounced ovarian enlargement is obtainable by such combined treatment

Highly purified preparations of FSH and LH from various sources (urine, blood, placenta, anterior-hypophysis) act essentially in the same manner.

In prepubertal, hibernating, or senile animals whose ovaries contain no mature follicles or corpora lutea, the effect of gonadotrophins is particularly striking. Yet in these, as in the normally cyclic adult animal, either FSH or LH results in the production of both follicles and corpora lutea, owing to complementary hormone production by the anterior-lobe

The precipitous development of follicles and corpora lutea may result in abnormal types of luteinization, for instance, corpora lutea with enclosed ova due to luteinization before ovulation could occur (so-called "atretic corpora lutea"); partial luteinization of the granulosa in a follicle in which other portions of the granulosa remain uninfluenced (so-called "abortive luteinization"); hemorrhages into the antra of maturing follicles or corpora lutea (so-called "blood spots")

It is noteworthy that in birds (e.g., fowl, pigeon) LH, unlike FSH, causes no ovarian stimulation and may actually inhibit the development of the gonad. This insensitivity to LH may be due to the fact that birds do not form corpora lutea.

The primate and particularly the human ovary is not as readily influenced by gonadotrophic preparations as that of most other animals. However, there is suggestive evidence that follicle maturation, ovulation and even corpus luteum formation may be obtained in women, if adequate doses are given at correct time intervals and especially if the injections are made intravenously, so that a high hormone concentration is obtained suddenly in the blood. — As judged by indirect evidence (pregnanediol excretion, endometrial histology), LH can cause premature luteinization of pre-existent follicles, or prolong the life-span of already formed corpora lutea in women. — Thus, depending upon the time of treatment it can either shorten or prolong the intermenstrual interval in patients with otherwise very regular cycles.

Chronic treatment with gonadotrophic preparations may cause complete involution of the gonads due to antihormone formation (see: Antihormones)

Local application of LH into the antrum of mature follicles results in the luteinization of these follicles only, while simple punctures without LH injections have no such effect This suggests that the gonadotrophic hormones act directly upon the follicles.

(4) *Luteotrophic hormone* tends to inhibit ovulation (especially in birds) and may result in an actual depression of ovarian weight Indeed, it inhibits even the effectiveness of concurrently administered, exogenous gonadotrophins However, it augments the life-span and luteoid hormone production of pre-existent corpora lutea

(5) *Gonadotrophic hormones plus folliculoids*, result in the formation of excessively large, "pregnancy type" corpora lutea, which sometimes may

take the form of voluminous corpus luteum cysts.

(6) *Other hypophyseal extracts*, including those of the middle and posterior-lobe, cause no specific ovarian lesions beyond those explicable on the basis of the non-specific damage produced by high doses.

Folliculoids, given in high concentrations over a short period of time, cause luteinization of pre-existent follicles and may even elicit precocious corpus luteum formation especially in the prepubertal rat. The resulting corpora lutea are unusually large, "pregnancy type," but do not persist very long, in spite of continued folliculoid administration. This effect is not obtained after hypophysectomy, unless anterior-pituitary extract is given with the folliculoids; presumably it is due to a peripheral synergism between folliculoids and luteotrophin.

Chronic treatment, even with small doses of folliculoids, causes pronounced ovarian atrophy. This is thought to be a compensatory atrophy due to inhibition of gonadotrophin formation in the pituitary.

Testoids given in very high concentrations, may likewise elicit a transitory formation of "pregnancy type," large corpora lutea (especially in the rat) In general, testoids tend to produce more mature follicles rather than corpora lutea, especially in the mouse. Perhaps some types of cystic ovaries in women may be due to excessive testoid production by the adrenal cortex, or by virilizing tumors

In embryonic and, less markedly, in immature postnatal ovaries, testoid treatment causes some "virilization of the ovary." It inhibits the development of the typically "female" cortex and stimulates the "male" medullary cords and rete tubules. Far-reaching transformations of this type have only been obtained in lower vertebrates (amphibia, birds) in which the testoids



Effect of estradiol on the rat ovary. Ovary of an adult rat which was treated with increasing doses (50 γ gradually raised to 200 γ) of estradiol, during a period of three months The animal was killed after an additional period of two [illegible] givei [illegible] necr [illegible] tion During [illegible] the cells of these theca-nests are transformed into atrophic "wheel cells", but after the two month rest period intense theca luteinization has occurred The experiment demonstrates the long persistence of the ovarian atrophy elicited by chronic folliculoid overdosage

were directly applied to the developing ovum However, some degree of ovarian ambisexuality is also seen in mammals following testoid administration to the pregnant mother. This explains the case of "*freemartin*" cattle. Here a female and a male twin have a common placental blood supply and under the influence of testoids elaborated by the male, the gonad of the female partner assumes ambisexual characteristics. The sterile and ambisexual "*tortoise-shell tomcat*" probably owes its gonadal anomaly to similar placental conditions.

LUTEOIDS (e.g., progesterone) and CORTICOIDS (e.g., desoxycorticosterone) are rather inactive in producing large corpora lutea or follicle cysts. All steroids exhibit this action approximately in proportion to their folliculoid potency. (See : "The Steroids.")

Continued treatment with high doses of various OTHER STEROID HORMONES also results in ovarian atrophy. Here again, it appears likely that the effect is due to the folliculoid potency of these compounds and acts through inhibition of gonadotrophin secretion.

HORMONALLY INACTIVE STEROIDS (e g , etiocholanolones, pregnanediol) cause no ovarian change.

Among the OTHER HORMONES, none exert a specific effect upon the ovary, although when given in toxic doses they all tend to inhibit follicle maturation and to produce ovarian atrophy as part of the general-adaptation-syndrome to their non-specific damaging effect

Diseases. — As may be expected, the various forms of HYPOPITUITARISM (e.g , pituitary dwarfism, Simmonds' disease, adiposogenital syndrome) cause involution or lack of development of the ovary Even the common ovarian involution with amenorrhea, produced by various non-specific damaging agents during the general-adaptation-syndrome, is probably of hypophyseal origin It presumably results from a diminished gonadotrophin secretion at times when there is a more urgent, vital need for an increased adrenotrophin production, the hypophysis being unable to elaborate both types of hormones in adequate amounts

HYPERPITUITARISM (e.g , acromegaly, Cushing's disease, etc) causes rather variable ovarian changes Gonadotrophin production may be normal, increased, or diminished, while the pituitary produces an excess of other anterior-lobe hormones.

HYDATIDIFORM MOLES and CHORIONEPITHELIOMAS are frequently accompanied by the formation of numerous, often cystic, large corpora lutea, and a great increase in the size of the ovaries due to the excessive production of gonadotrophins by the tumor tissue.

In the ADRENOGENITAL SYNDROME the ovaries are usually undeveloped, in spite of the striking precocious uterine bleeding and sex-organ differentiation.

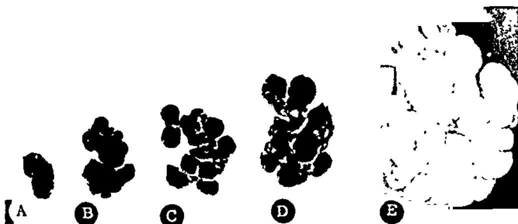
In TRUE PRECOCIOUS PUBERTY, there is a balanced and otherwise normal, but premature gonadotrophin formation by the pituitary; correspondingly the ovaries are similar to those of normal adult women. Children who are the bearers of such ovaries may become fertile at an unusually early age. In one case (described by *Escomel*) a girl of 5 years and 8 months gave birth to a healthy living infant.

BRAIN LESIONS, especially tumors of the pineal region or hydrocephalus, may produce precocious pseudopuberty with premature uterine bleeding The ovaries rarely reveal any sign of precocious maturation, although sometimes they show "small cystic degeneration" (see · Diseases of the Ovaries) The mechanism of this type of pseudopuberty is still unknown.

In women with FIBROMYOMAS of the uterus, persistent follicles or unusually large corpora lutea are common Some investigators believe that hyperfolliculoidism is an important factor in fibromyoma formation

OTHER DISEASES are not known to act upon the ovaries directly. However, in most women with serious, chronic diseases, follicle maturation and corpus luteum formation are disturbed, and the cycles become irregular, or chronic amenorrhea sets in as a result of the general-adaptation-syndrome elicited by the accompanying non-specific damage.

The ovarian lesions which are typical of the various clinical forms of HYPO-or



Appearance of rat ovary under various conditions. — A. Ovary (4 mg) of untreated 2-week-old rat. Note absence of mature follicles and corpora lutea — B. Ovary of adult untreated rat (16 mg). Note several normal sized corpora lutea. — C. Ovary on 14th day of lactation (26 mg) Note one set of fully developed corpora lutea, which are hardly much larger than those of the cycle — D. Ovary of pregnant rat (about 14th day of gestation) (47 mg) Note that number of corpora lutea is not increased and corresponds to that formed during average cycle. Si[illegible] ented however several, very small follicles (greyish [illegible] development of corpora lutea ("mulberry ovary") [illegible] /day of PMS for 10 days during lactation (308 mg [illegible] not very different from those seen in normal lactation (smaller than those of pregnancy)

HYPEROVARIANISM are discussed in the sections devoted to the latter.

Diet.— The ovary is especially sensitive to qualitative or quantitative changes in food intake. Prolonged FASTING OF UNDERNUTRITION causes atrophy of the gonads in various animal species. Only in certain fish is the development of the ovary remarkably independent of food intake Thus, for instance the salmon swims upstream and takes no food during the breeding season, although it performs very active muscular exercise. The animal loses weight, while its ovaries enlarge so much that instead of the initial 0.4%, they constitute 27% of the total body weight. In women, prolonged malnutrition leads to fibrosis and atrophy of the ovaries. Mature follicles are absent and the interstitial cells become atrophic.

On the other hand, OVERFEEDING and various QUALITATIVELY INADEQUATE DIETS (vitamin, amico-acid, protein, salt deficiencies, etc) likewise interfere with the sexual cycle by causing ovarian atrophy Here again, the increased production of corticotrophin and perhaps also of other pituitary hormones, during the resulting general-adaptation-syndrome, probably occurs at the expense of a diminished gonadotrophin production during the period of strain.

Certain diets, however, may exert a specific influence upon the ovaries. Thus, rats fed predominantly on LENTILS — or some of the other leguminous seeds — develop ovarian atrophy with persistent diestrus, perhaps due to the presence in such plants of a specific ovario-toxic substance (phaseolin).

Contrary to the marked degenerative changes observed in male gonads, the ovaries of VITAMIN-E DEFICIENT animals are of normal appearance The sterility of such animals is merely due to embryo resorption during pregnancy.

Nervous Stimuli. — COPULATION OR STIMULATION OF THE UTERINE CER-

vix causes pseudopregnancy in a variety of animal species (e.g., rat, rabbit, cat); this is accompanied by the formation of a persistent, functional corpus luteum. Here a single nervous stimulus suffices to produce endocrine changes which maintain the corpus luteum for a period of several weeks. The length of pseudopregnancy varies in the different animal species.

In the human female, follicle rupture is usually spontaneous, but some investigators believe that occasionally, ovulation may be provoked by sexual intercourse. In very exceptional cases, the corpus luteum may persist for several months, so that pseudopregnancy results. It has also been claimed that excessive sexual intercourse or masturbation may cause cystic degeneration of the ovaries or the formation of persistent follicles. In such instances, it is difficult to determine however, whether hyperfolliculoidism due to persistent, cystic follicles was not the cause, rather than the result, of the excessive sexual activity.

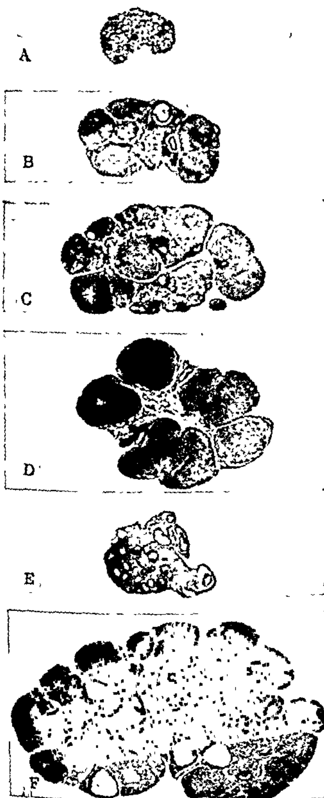
An interesting note illustrating the action of psychic stimuli upon the ovary has been published by *LeConte*, in 1884. He relates the case of two negresses who were struck by lightning. In one of them, a young woman, menstruation ceased completely after the accident, while in the other, a woman over 70 years of age who had not menstruated for 20 years, regular cycles reappeared every month for more than a year and her breasts enlarged considerably following the shock Some gynecologists believe that while pleasant sensations elicited by sexual intercourse may provoke ovulation, disgust or fear of cohabitation can inhibit it This may explain the sterility of certain marriages in which both partners prove to be fertile in subsequent marriages to other mates. Prolonged amenorrhea is frequent in women who are afraid of pregnancy, but the underlying ovarian changes have not yet been studied such cases.

The NERVOUS STIMULATION OF TI NIPPLES by the offspring is responsib for the persistence of the so-called co pora lutea of lactation. That these co pora lutea are not maintained owin to milk production has been shown b experiments on the rat in which th milk ducts (galactophores) were transected, but the young were allowed to continue nursing. Although milk could obviously not be secreted, the nervous stimulus in itself sufficed to maintain the corpora lutea in a functional condition. Unlike the stimulus of copulation, that of nursing must be continuous in order to maintain the corpora lutea of pseudopregnancy. (See: Pseudopregnancy.)

Complete DENERVATION OF THE OVARIES does not interfere with the production of follicles, corpora lutea of the cycle, or even corpora lutea of pregnancy.

TRANSECTION OF THE PITUITARY STALK before or immediately after copulation prevents ovulation in the rabbit. On the other hand, LOCAL ANESTHESIA OF THE VAGINA AND VULVA or even complete ablation of the upper portion of the vagina and uterus do not prevent postcoital ovulation in rabbits. It was concluded that local nervous stimuli in the genital region are not essential for the copulatory reflex. Apparently, psychic stimulation alone suffices to elicit nervous impulses which pass down to the pituitary across the hypophyseal stalk. Such emotional stimuli must also be invoked to explain the pseudopregnancy produced in rabbits by merely showing them a male kept in an adjacent, but separate, cage.

Age. — Follicle maturation and corpus luteum formation commence at puberty. Usually the first few cycles are rather irregular and in some animals, as well as in women, they may be anovular



Appearance of the rat ovary under various experimental conditions. — A. Ovary of a normal 3-week-old rat. Note immature aspect of the ovary with no large follicles and no corpora lutea. (Same low magnification as fig B-F) — B. Ovary of a normal adult rat Note several large corpora lutea and one almost mature follicle with distinctly visible cumulus oophorus and ovum — C. Ovary of a normal rat on the 16th day of lactation No mature follicles but well-developed, medium sized, corpora lutea of lactation — D. Ovary of a rat on 16th day of lactation following treatment with 1 mg/day of estradiol commencing immediately after delivery Note greatly enlarged corpora lutea (compare with fig C), but no formation of new corpora lutea Milk secretion was arrested under the influence of this folliculoid therapy — E Ovary of an adult rat treated with increasing doses of estradiol (beginning with 50 γ/day and raised to 200 γ/day) during a period of three months. The picture was taken two months after discontinuation of this prolonged folliculoid treatment, but ovarian atrophy was still severe Note that general aspect of the ovary resembles that of an immature rat (compare with fig A) Part of the oviduct is also shown in this picture to demonstrate marked fibrosis and thickening of its wall — While brief treatment with massive doses of folliculoids causes enlargement of preexistent corpora lutea (fig. D) prolonged administration of even smaller doses causes severe ovarian atrophy, which persists after discontinuation of therapy — F. Ovary of an adult rat following treatment with increasing doses of LH (150 I U/day gradually raised to 450 I U/day) Note typical appearance of 'mulberry ovary' with numerous, but not particularly large corpora lutea

Compare these histologic pictures with the macroscopic specimens reproduced on page 381

VIX causes pseudopregnancy in a variety of animal species (e.g., rat, rabbit, cat); this is accompanied by the formation of a persistent, functional corpus *luteum*. *Here a single nervous stimulus* suffices to produce endocrine changes which maintain the corpus luteum for a period of several weeks. The length of pseudopregnancy varies in the different *animal species*.

In the human female, follicle rupture is usually spontaneous, but some investigators believe that occasionally, ovulation may be provoked by sexual intercourse. In very *exceptional cases*, the corpus luteum may persist for several months, so that pseudopregnancy results. *It has also been claimed that* excessive sexual intercourse or masturbation may cause cystic degeneration of the ovaries or the formation of persistent follicles. In such instances, it is *difficult to determine however, whether* hyperfolliculoidism due to persistent, cystic follicles was not the cause, rather than the result, of the excessive sexual activity.

An interesting note illustrating the action of psychic stimuli upon the ovary has been published by *LeConte*, in 1884. *He relates the case of two negresses* who were struck by lightning. In one of them, a young woman, menstruation ceased completely after the accident, while in the other, a woman over 70 years of age who had not menstruated for 20 years, regular cycles reappeared every month for more than *a year and her breasts enlarged considerably* following the shock. Some gynecologists believe that while pleasant sensations elicited by sexual intercourse may provoke ovulation, disgust or fear of cohabitation can inhibit it. This may explain the sterility of certain marriages in which both partners prove *to be fertile in* subsequent marriages to other mates. Prolonged amenorrhea is frequent in women who are afraid of pregnancy, but the *underlying ovarian* changes have not yet been studied in such cases.

The NERVOUS STIMULATION OF THE NIPPLES by the offspring is responsible for the persistence of the so-called corpora lutea of lactation. That these corpora lutea are not maintained owing to milk production has been shown by experiments on the rat in which the *milk ducts (galactophores)* were transected, but the young were allowed to continue nursing. Although milk could obviously not be secreted, the nervous

[illegible]

that of nursing must be continuous in order to maintain *the corpora lutea* of pseudopregnancy. (See : Pseudopregnancy.)

Complete DENERVATION OF THE OVARIES does not interfere with the production *of follicles*, corpora lutea of the cycle, or even corpora lutea of pregnancy.

TRANSECTION OF THE *PITUITARY* STALK before or immediately after copulation prevents ovulation in the rabbit. On the other hand, LOCAL ANESTHESIA OF THE VAGINA AND VULVA or *even complete* ablation of the upper portion of the vagina and uterus do not prevent postcoital ovulation in rabbits. It was concluded *that local* nervous stimuli in the genital region are not essential for the copulatory reflex. Apparently, psychic stimulation *alone* suffices to elicit nervous impulses which pass down to the pituitary across the hypophyseal stalk. Such emotional stimuli must also be invoked to explain *the pseudopregnancy* produced in rabbits by merely showing them a male kept in an adjacent, but separate, cage.

Age. — Follicle maturation *and* corpus luteum formation commence at puberty. Usually the first few cycles are rather irregular and in some animals, as well as in women, they may be anovular.

In man, treatment of the ovary with moderate doses of X-rays is frequently used as a therapeutic measure to produce temporary amenorrhea. Minute doses of X-rays are said to stimulate the ovaries and occasionally, to reinitiate menstrual cycles in women suffering from amenorrhea. Heavy X-ray treatment on the other hand, causes permanent ovarian involution and cessation of menstrual cycles with sterility.

In certain animals, LIGHT RAYS play a very important rôle in the regulation of ovarian activity. In the brook trout, spawning may be induced prematurely by exposure to light. In the salamander, ovulation fails to occur as long as the animals are kept in the dark. In the duck, pheasant, sparrow, etc., egg-laying may be induced by exposure to light both in the immature and (during the off-season) in the mature female (*Benoit, Roan, Bissonnette*). In most mammals however, light rays exert no marked influence upon ovarian development, except perhaps in the ferret and a few other species with seasonal estrus.

It is most probable that light stimuli reach the pituitary through the stalk.

Other Stimuli. — CLIMATE, CAPTIVITY, TEMPERATURE VARIATIONS, EXCESSIVE MUSCULAR WORK, HEMORRHAGE, BURNS, TRAUMA and other non-specific agents capable of eliciting a general-adaptation-syndrome all tend to cause irregularities in ovarian function, usually accompanied by ovarian atrophy. None of these factors have been proven to exert a specific effect, that is, one unaccounted for by the disturbance in hormone production due to the resulting general-adaptation-syndrome.

OVARIAN DISEASES IN GENERAL

DEFINITION

In this chapter we shall briefly consider conjointly all those diseases which result from changes in the ovaries. In contradistinction to other glands, it is impractical in the case of the female gonad to strictly distinguish between hypo- and hyperfunctional diseases. Hyperfunction of one part of the ovary (e g., a follicle cyst causing hyperfolliculoidism) may be associated with hypofunction in other respects (in the above example for instance, lack of corpus luteum formation). Hence we shall use this chapter on Ovarian Diseases in General, to outline briefly the changes produced in the various organs by hypo- or hyperfunction of the ovary, or one of its parts Here we shall also discuss general problems (e.g., classification, pathogenesis, complications, diagnosis, prognosis and therapy) which are applicable to several ovarian diseases. The reader will be referred to other chapters for a more complete description of specific syndromes

CLASSIFICATION

It is customary to classify the ovarian syndromes according to their most prominent clinical manifestations. Thus amenorrhea, menorrhagia, or dysmenorrhea are often considered as distinct clinical entities irrespective of their etiology This may be adequate from a purely clinical viewpoint but in this book we are using the following classification

I. OVARIAN DISEASES IN GENERAL:
- Definition.
- Classification.
- Pathogenesis.
- Clinical Course.
  - State and Metabolism.
  - Growth and Bone Structure.
  - Blood.
  - Cardiovascular System.
  - Nervous System (dysmenorrhea, intermenstrual pain, ovaralgia, sense organ lesions).

The ovarian weight in man is about 0.3 gm. at birth. At this time several fairly mature follicles may be distinguishable, presumably due to exposure of the embryonic gonads to the large quantities of maternal gonadotrophins. The ovarian weight at 6-10 years is 2 gm. and at puberty, about 7 gm. Even after puberty, it tends to increase to about 10-12 gm. by the 21st-30th year, but subsequently it decreases to about 4 gm. in senile women. About three to four years after the menopause, no follicles are distinguishable, although the germinal epithelium remains intact. Sclerotic changes in the ovarian vessels are especially conspicuous in the aged

Constitution, Race and Heredity. — Constitutional and racial factors play a rôle in ovarian development in animals and man. The claim that puberty tends to occur earlier in southern than in northern races is not clearly supported by statistics, but unusually early or late puberty is frequently seen as a familial characteristic. In uniovular twins, the menstrual cycles of both sisters often run synchronously.

In the dwarf mouse, ovulation does not occur under normal conditions, and consequently there are no corpora lutea. Certain breeds of sheep possess the ability to reproduce consistently at higher rates than others, and twinning in sheep is possibly also inheritable.

Sex. — The effect of SEXUAL INTERCOURSE upon the development of the ovary has been discussed above under "Nervous Stimuli"; the changes corresponding to the phases of the SEXUAL CYCLE will be considered in the chapter on Estrus and Menstruation.

Pregnancy and Lactation. — The ovarian changes characteristic of pregnancy and lactation are discussed in the sections specifically devoted to these conditions.

Season. — Seasonal variations in ovarian development are especially important in amphibia, reptiles, birds, and hibernating mammals in which the ovaries undergo atrophy during the resting season. For instance in the bat, ovulation occurs in the spring, while during hibernation the gonad is inactive and small.

Some non-hibernating mammals (e.g. dog, sheep) likewise produce mature follicles only during certain seasons of the year.

In the human female, seasonal variations have no marked effect upon the ovarian cycle.

Rays. — X-RAYS are especially damaging to the granulosa cells, which can be selectively destroyed by them. In the mouse, suitable X-ray treatment may lead to the complete disappearance of all follicles and corpora lutea, while the estrus cycles continue (*Parkes*) This shows that folliculoids can be produced in the absence of granulosa cells or corpora lutea. If immature mice are exposed to a full sterilizing dose of X-rays, irradiation is followed by complete degeneration of all granulosa cells and ovocytes. The germinal epithelium proliferates and forms epithelial cords. In the adult animal, the entire ovary may then be composed of the cords of this first proliferation, which tend to transform themselves into luteal tissue. In many cases, a second proliferation of small, spherical, slightly elongated cords occurs from the germinal epithelium These resemble the so-called spermatic cords described in the ovaries of inbred rabbits and freemartin cattle. Even the ovaries of mice X-rayed in utero, show similar changes.

In certain strains of mice, X-ray treatment of the ovaries induces a very high incidence of folliculoid-producing (permanent estrus) transplantable granulosa-cell tumors (*Furth and Butterworth*)

Corpora lutea are much more resistent to X-rays than are follicles, as shown by experiments on lactating mice.

Growth and Bone Structure. — Although chronic treatment with folliculoids may cause increased bone deposition with osteosclerosis in experimental animals and perhaps even in women, spontaneous diseases of the ovary are rarely accompanied by typical skeletal lesions. OSTEOMALACIA — a disease characterized by deficient calcification of osteoid tissue — had previously been considered to result from ovarian hyperactivity and it was claimed that many patients improved following castration. It is now generally recognized, however, that osteomalacia is merely the adult counterpart of rickets, and as such, is due to a nutritional deficiency. Yet the disease is much more frequent in women than in men and hence the possibility of some ovarian influence cannot be excluded completely. The strain on calcium metabolism occasioned by repeated pregnancies and lactations is probably of importance.

Blood. — Various types of ANEMIA associated with ovarian diseases are most frequently due to the chronic loss of blood from the uterus. "CHLOROSIS VIRGINUM," a special type of anemia which occurred almost exclusively in pre-adolescent girls, had been regarded as due to ovarian insufficiency This etiology has not been proven however, and the disease, prevalent during the 19th Century, seems to have disappeared almost completely It was probably due to inadequate hygienic conditions, undernutrition and pubertal hemorrhages rather than to any specific ovarian malfunction.

HEMOPHILIA is an hereditary disease in which the coagulation-time of the blood is considerably prolonged. This disease is transmitted only by women, but is manifest only in men. It is claimed that the women of hemophiliac families are particularly fertile and predominantly produce male children who do not transmit the disease It is very doubtful that ovarian hormones play any direct rôle in this condition and contrary to the expectations of some authors, ovarian hormones exert no significant beneficial effect.

Cardiovascular System. — Ovarian diseases cause no characteristic cardiovascular symptoms, except those due to pressure by very large ovarian tumors, which may result in cardiac decompensation, edema in the lower extremities, etc. Congenital malformations of the ovary are often accompanied by malformations of the cardiovascular system.

The characteristic menopausal hypertension and flushes are discussed in the chapter . *Diseases of the Menopause*.

Nervous System. — Nervous disturbances are very common accompaniments of ovarian disease. EMOTIONAL INSTABILITY and even severe HYSTERIA may appear in women who suffer from chronic ovarian or uterine disease, due to a sense of sexual inferiority derived from the abnormal bleeding, sterility, etc. Even the name of hysteria is derived from "hystera," the Greek word for uterus, since ancient physicians sought the cause of the disease in that organ. FRIGIDITY and lack of libido are also frequent, but usually due to psychologic causes rather than to a diminished folliculoid hormone production; however, folliculoids, luteoids and testoids likewise play a rôle in conditioning the female libido.

The most important nervous manifestations of ovarian disease are those associated with pain Among these we distinguish the following :

DYSMENORRHEA, which merely means painful menstruation. The pain in primary dysmenorrhea (see below) is usually of a colicky, laborlike nature in contrast to the mostly dull pain of secondary dysmenorrhea. Indeed, the pain may be so severe that nausea with vomiting ensue and the patient becomes bedridden for several days every month. It may begin one or two days before the onset of the flow, persisting

Digestive System.
Skin.
Urinary System.
Accessory Genital Organs (lesions in the oviduct, amenorrhea, oligomenorrhea, hypomenorrhea, retention of menses, polymenorrhea, menorrhagia, midmenstrual bleeding, metrorrhagia, changes in the vagina, changes in the mammary glands).
Sterility.
Complications.
Diagnosis.
Therapy.

II. SPECIAL DISEASES OF THE OVARY:
Malformations and Anomalies (inc. ambisexuality).
Hernia and Prolapse.
Torsion.
Retrogressive Changes.
Vascular Disturbances.
Lymphangiectases.
Inflammations.
Tumors.

III. DISEASES OF THE SEXUAL CYCLE:
Diseases of the Pubertal Period (puberty hemorrhages, precocious and delayed puberty).
Diseases of the Menopause.
Derangements of the Correlation Between Ovulation and Menstruation or Estrus (Amenstrual Ovulation, Anovular Menstruation).
Vicarious Menstruation.

IV. DISEASES OF PREGNANCY
Group IV will be considered in the chapter "Pregnancy" of the section "Correlations."

PATHOGENESIS

In general, ovarian syndromes are due to one of the following three causes:

(1) PRIMARY LESIONS OF THE OVARY For instance, aplasia, destruction by local diseases, tumors causing hypo- or hyperactivity, can be the cause of ovarian malfunction.

(2) PRIMARY LESIONS OF THE PITUITARY or disturbances in the normal interaction between pituitary and ovary. Thus, destruction of the pituitary in Simmonds' disease causes atrophy of the ovaries because of the resulting lack of gonadotrophins; hyperplasia or tumor formation in the anterior-lobe may result in a variety of ovarian lesions, depending upon the resulting increase or decrease in gonadotrophin production; disturbances in the normal interaction between pituitary and ovary may cause anomalies of the sexual cycle.

(3) CHANGES IN THE INTERNAL OR EXTERNAL ENVIRONMENT. As part of the general-adaptation-syndrome which is elicited by most of the spontaneous diseases (including malfunctions of other endocrine glands), exposure to stress, malnutrition or even emotional upset, the gonadotrophin elaboration by the hypophysis may be so altered as to cause ovarian changes with derangements of gonadal hormone production.

CLINICAL COURSE

State and Metabolism. — In spite of the manifold systemic effects of ovarian hormones, the diseases of the ovary are generally not accompanied by any characteristic and uniform disturbances in the general condition of the patient. The so-called "FACIES OVARIANA," a drawn-out, tired facial expression, is not especially typical of ovarian diseases. It probably results from the continued effect of pain, repeated loss of blood, etc., which so frequently accompany ovarian diseases.

Slight water retention, with a corresponding gain in weight, occurs normally prior to or at menstruation in many women. When this is exaggerated we speak of *"premenstrual"* or *"menstrual edema"* The etiology of the condition is still unknown, but it is probably of endocrine origin. Treatment with a salt-diuretic, such as ammonium chloride is often very useful.

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OVARALGIA (from the Greek : algos = pain) merely means pain in the ovary. It is frequently due to small-cystic degeneration, endometriosis of the ovary (see corresponding chapters), or to inflammatory lesions. Certain types of *intermenstrual pain* are transient instances of ovaralgia. The condition has no uniform etiology.

MENSTRUAL HEADACHE (or MIGRAINE) and EPILEPSY have been interpreted as of endocrine origin because of their relationship to the cycle, but too little is known about their etiology to warrant a detailed discussion here. Premenstrual treatment with luteoids or folliculoids is often beneficial. They may be due to vasomotor disturbances or transient slight edema of the brain, temporary enlargement of the hypophysis, etc.

"PREMENSTRUAL TENSION" is a condition of extreme nervous irritability, sometimes with emotional outbursts, compulsive ideas, etc., which occur before the onset of bleeding It has been ascribed to abnormal sodium retention and subsequent brain edema due to a hormonal derangement. As in the closely allied premenstrual edema, ammonium chloride often brings relief

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By contiguity, appendicitis may lead to oophoritis and vice versa. These possibilities should be kept in mind, in connection with the sometimes difficult problem of a differential diagnosis between appendicitis and ovarian lesions

Skin. — Ovarian diseases undoubtedly exert an important action upon the skin. The so-called "CHLOASMA UTERINUM" (light brown, irregular patches on the skin, especially of the face) occur frequently in pregnancy and in connection with diseases of the ovaries, perhaps because of the well-known effect of folliculoids upon pigmentation.

SCLERODERMA is sometimes associated with ovarian disease, as are various other skin lesions, especially those of the ALLERGIC type.

Urinary System. — The urinary system is rarely involved in ovarian disease, except by mere contiguity (spreading of inflammatory or neoplastic processes, endometriosis, etc., from the ovarian surface to the bladder), or direct compression of the bl[illegible]der or ureters by ovarian

Accessory Sex Organs. [illegible] diseases may affect the TUBES either by direct [illegible] through the intermediary of [illegible] hormones which influence [illegible] morphologic development and

until the first or second day of the period; often it commences simultaneously with menstruation, and sometimes it continues throughout the period.

Most authors distinguish primary (essential, functional or intrinsic) dysmenorrhea due to functional factors from secondary dysmenorrhea, in which the pain is explicable by the accompanying morphologic lesions (inflammations, neoplasms, endometriosis, uterine displacement, lesions in the bladder, the ureter or in the sacro-iliac joints, etc.). In this chapter we shall limit our discussion to functional dysmenorrhea. Its etiology is still unknown, but the following factors have been considered :

(1) *The hormonal control of uterine motility* The uterus undergoes contractions and relaxations throughout the cycle, and it is known that both folliculoid and luteoid hormones influence this contractility. It has not been possible to determine exactly what hormonal disturbance if any, is responsible for the painful contractions. The fact that dysmenorrhea may be beneficially influenced by various hormone preparations, and that pain is often limited to a certain phase of the cycle, speaks in favor of the conception that hormonal stimuli play an important rôle. Many gynecologists believe that functional dysmenorrhea never occurs in the absence of ovulation.

(2) *The development of the uterus* In most patients dysmenorrhea is associated with hypoplasia of the uterus frequently accompanied by infantilism or displacement. Since contractions of anoxic muscles tend to be painful, it has been assumed that inadequacies in the blood supply to the myometrium may elicit pain by causing temporary anoxemia of the muscles during contractions.

(3) *Nervous factors* Dysmenorrhea is particularly common in high-strung, nervous women, although the phlegmatic type is by no means immune; frequently nervous excitability is the result, not the cause, of constant dysmenorrhea. Some investigators ascribe a prominent rôle to changes in the nerve fibers and ganglia of the uterus.

(4) *Passage of large fragments through the uterine canal.* The internal os is extremely sensitive to dilatation and the passage of large tissue fragments and blood clots through a resistant uterine canal may cause painful cramps during menstruation. The so-called "membranous" dysmenorrhea is due to the passage of large, undissolved fragments of uterine lining and represents the most clear-cut case of this type. Anteflexion of the uterus, with a kink in the cervix region, predisposes to the so-called "obstructive dysmenorrhea." It is doubtful however, whether similar mechanical causes are operative in the usual cases of functional dysmenorrhea

(5) *Gastrointestinal disorders.* In many cases there is evidence suggesting that the cramps are of gastrointestinal origin, there is constipation during the premenstrual period, the pain being accompanied by a desire to defecate and the passage of hard stools, from which laxatives bring relief.

In any event, it is quite improbable that all types of menstrual pain could be ascribed to a uniform etiology Dysmenorrhea is a symptom, not a disease. Even the distinction between primary and secondary dysmenorrhea is somewhat artificial, since as soon as the etiology of a certain type is recognized, we shift it from the first to the second category.

INTERMENSTRUAL PAIN (MITTELSCHMERZ) is a pain of varying intensity, which occurs approximately at the mid-interval between two menses. It usually lasts from a few hours to one or two days and is sometimes, but not invariably, accompanied by bleeding. The condition has variously been ascribed

to : rapid growth of, or bleeding from, the ovulating follicle (this has sometimes been demonstrated by biopsy); a temporary drop in folliculoid hormone formation at the middle of the cycle; a hormonal disturbance in the contractility of the uterus or the oviduct, or to adhesions between the ovary and other peritoneal organs which could be stretched and torn at the time of follicle rupture. It is very probable that several, if not all, of these factors, can be conducive to intermenstrual pain.

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Accessory Sex Organs. — Ovarian diseases may affect the FALLOPIAN TUBES either by direct contact, or through the intermediary of the ovarian hormones which influence both the morphologic development and the con-

tractility of the oviducts. However, changes in the tubes rarely play an important part in the general syndrome.

One of the most frequent accompaniments of ovarian disease is a derangement in the menstrual flow. We distinguish the following main types:

(1) Amenorrhea, that is, absence of menstruation. In *primary amenorrhea*, menstruation has never occurred. Since in cases of delayed puberty the first bleeding may not appear until the 18th year of age, it is incorrect to speak of primary amenorrhea in patients under that age. This condition may occur as a result of an endocrine derangement (aplasia, hypoplasia, degeneration of the ovaries or pituitary, etc.), or it may be merely due to anomalies of the uterus itself.

In *secondary amenorrhea*, a previously established menstrual cycle ceases before the normal age (45-50 years) of the menopause. Surgical or X-ray castration, persistent corpora lutea, destruction of the pituitary or the ovaries by disease, systemic intoxications, infections, nutritional deficiencies, or even purely emotional disturbances may cause secondary amenorrhea; indeed, any chronic exposure to stress can abolish the menstrual cycle, due to the decrease in gonadotrophin secretion during the ensuing general-adaptation-syndrome.

(2) Oligomenorrhea is a condition in which menstrual bleeding occurs rarely and usually at irregular intervals. There is no clear distinction between temporary amenorrhea and oligomenorrhea. Rarity of menstrual bleeding appears to be due to a disturbance in the normal interrelationships between the pituitary and the ovary, but the exact mechanism of its pathogenesis is unknown, and probably diverse disturbances may lead to this symptom. Oligomenorrhea is not incompatible with good health and fertility.

(3) Hypomenorrhea is a condition in which the menstrual bleeding is quantitatively deficient, although the length of the cycle, the progestational transformation of the endometrium, and even fertility may remain normal. It is common in hypothyroidism and in various types of ovarian insufficiency, especially those of the pre-climacteric age. Sometimes partial destruction of the endometrium by disease or partial hysterectomy causes hypomenorrhea. Quite frequently the condition is associated with oligomenorrhea.

(4) Retention of menses (or cryptomenorrhea) is a condition in which menstruation proceeds normally, but the flow does not make its way to the exterior because of an obstruction in the cervical canal, or an imperforate hymen. It should not be confused with amenorrhea. Retention of the menses is not an endocrine disease, but merely due to a malformation of the genital passages. It often leads to the accumulation of menstrual blood and subsequent cystic dilatation of the uterus or vagina, and predisposes to the backflow of endometrial particles through the oviducts into the peritoneum; thus, it may give rise to internal endometriosis.

(5) Polymenorrhea is a condition in which the menstrual intervals are shortened, but the cycle is otherwise normal. In the majority of the cases, it is probably due to premature ovulation or early involution of the corpus luteum; correspondingly either the follicular or the luteal phase is shortened. Various types of pelvic inflammations, uterine fibromyomas, hypo- or hyperthyroidism and even purely emotional factors, such as fear of pregnancy, have been claimed to cause polymenorrhea.

(6) Menorrhagia (or hypermenorrhea) is a condition in which menstruation is more abundant and of longer duration than normal. It is often, though not always, accompanied

by polymenorrhea. Its main danger lies in the constant loss of considerable quantities of blood. It occurs in connection with hypothyroidism or hyperthyroidism; organic lesions in the pelvis (adenomyomas, salpingitis, subinvolution of the uterus, cardiac decompensation), or as a result of various blood *diseases*.

(7) METRORRHAGIA is a condition in which uterine bleeding is frequent and irregular. It is often caused by bleeding uterine neoplasms (polyps, cancers, fibromyomas, etc.), retained placental remnants, or endometrial inflammations. Its most common endocrine cause is hyperfolliculoidism, due to persistent cystic follicles which lead to metropathia hemorrhagica (see: Metropathia on pp. 426, 427). Like menorrhagia, it may also lead to severe anemia, due to the constant loss of blood.

(8) INTERMENSTRUAL (OR MIDMENSTRUAL) BLEEDING is a condition in which, usually slight, uterine bleeding (sometimes *only a few spots* of a brownish discharge) occurs between otherwise regular menstrual periods It is frequently associated with intermenstrual pain. These scanty flows are often regularly interpolated between the normal *periods* and *occur at ovulation* time. In the German literature, the term "kleine Regel" (little period) has been applied to this condition. It corresponds to the uterine hemorrhage which occurs at estrus in some animals (e.g., *dog*), *and probably results from* small hemorrhages in an excessively stimulated follicular-phase-type of endometrium. It is not necessarily associated with any severe derangement in sexual functions and is compatible with *normal fertility*.

CHANGES IN THE VAGINA are comparatively unimportant accompaniments of ovarian disease. With the use of the vaginal smear method it is possible to estimate approximately the ovarian hormone *production In amenorrhea* due to ovarian failure, nucleated cells predominate, while, in hyperfolliculoidism most of the cells in the vaginal smears are cornified. Ovarian failure predisposes the vaginal epithelium to infections, *since it reduces its resistance* against micro-organisms. Sometimes deficient cornification *renders the vagina hypersensitive and causes dyspareunia*.

CHANGES IN THE MAMMARY GLANDS are common consequences of ovarian disease. *Underdevelopment of the breasts* is often the result of ovarian deficiency, *but it may occur in women* whose cycles and fertility are normal. In these cases *it is perhaps* due to a relative ovarian hormone insensitivity of the pituitary (decreased mammogenic hormone production) or of the mammary tissue itself.

Hypertrophy of the breasts often occurs at puberty (pubertal hypertrophy) and may persist throughout life. The breasts may become so large as to hang below the waist line. This may be due to excessive production of ovarian hormones *or to an exaggerated* hormone-sensitivity of the pituitary or breast tissue.

Chronic cystic mastitis (cyclomastopathy) is a *condition which appears* in two main forms: in one there is simple cystic dilatation of the galactophores (cystic form); in the other proliferation of the duct epithelium predominates (Schimmelbusch's disease, Reclus' disease, *adenosis*). *In these latter* cases, differentiation from malignancy may become difficult.

Cystic mastitis is especially common between 30 and 45 years of age, but it may occur in younger women. Usually *it disappears after the menopause*, presumably due to diminished ovarian hormone secretion, or even before that time without obvious reasons. It has a tendency to undergo periodic exacerbations and remissions. The breasts are *often enlarged and localized* cysts and

nodules are readily detectable by palpation. The etiology of this condition is not known. There may be an increased ovarian or hypophyseal hormone production, or an excessive hormone sensitivity of the breast.

Sterility and Infertility. — Sterility is often defined as the inability to conceive, while, in infertility, pregnancy can be initiated, but is terminated by abortion. It is customary to distinguish *primary* sterility in which conception has never occurred, from the *secondary* type, in which conceptions have taken place at an earlier time.

Here, we shall only consider the female factor in sterility and infertility. In order to permit insemination, it is manifestly necessary that the ovaries produce normal ova and discharge them from the ovarian surface into the tubal orifice, through which they must migrate without meeting an obstruction. Similarly, the spermatozoa must find favorable conditions in the vagina, the cervical canal and the oviduct: that is, the passages through which they have to ascend, in order to fertilize the ovum in the tube Finally the endometrium must be progestational to permit implantation of the ovum, and the developing embryo must remain under favorable humoral conditions; thus, for *example, during the first stages of development* it is greatly dependent upon an adequate maternal progesterone supply.

VARIOUS TYPES OF STRESS may interfere with normal ovulation and menstruation (infectious diseases, alcoholism, dietary insufficiencies, emotional factors), and the same is true of ENDOCRINE DISTURBANCES, *especially* hypopituitarism, hypo- or hyperthyroidism, etc. Sterility can also be occasioned by COITAL DIFFICULTIES, such as dyspareunia (*pain during* sexual intercourse). This may be caused by psychologic reasons, trichomonas infection, senile vaginitis, inflammatory lesions in the pelvis, endometriosis, malformations, or occlusion of the genital passages due to developmental anomalies, inflammatory lesions, etc.

COMPLICATIONS

Among the complications of ovarian diseases, the most important is CHRONIC SECONDARY ANEMIA, due to continuous loss of blood through exaggerated menstrual bleeding. Occasionally, the rupture of large, cystic follicles into the peritoneum may lead to severe PERITONEAL HEMORRHAGES; rupture of an ovarian abscess to PERITONITIS, etc., but in general, ovarian diseases do not tend to cause important complications.

DIAGNOSIS

In the diagnosis of ovarian disease, it is important to inquire into the FAMILY HISTORY, since many diseases tend to be transmitted from the parents to the offspring.

The PAST HISTORY OF THE PATIENT furnishes valuable data concerning the onset of menstrual bleeding (menarche), the duration of the flow, the length of the intervals between menses, the amount of menstrual blood, the character of the discharge (with special reference to the presence of clots, membranes and bright red blood which are *abnormal*), *intermenstrual* bleeding and pain, dysmenorrhea, and the date of the last menstrual period The marital history of the patient, the type of vaginal discharge (if any), urological symptoms (pain, increased *frequency*, hematuria, etc), and the development of the PRESENT ILLNESS must also be recorded

SYSTEMIC PHYSICAL EXAMINATION should be directed towards the detection of infectious, nutritional, endocrine, and other general diseases which may have an effect upon ovarian function

GYNECOLOGIC EXAMINATION will help to reveal the presence of inflam-

Schematic drawing summarizing chief causes of uterine bleeding.
(After E Henriksen Am J of Obst and Gynec *41* 179 1941)



Sterility due to malformation of the uterus. X-ray following injection of the uterus with X-ray opaque fluid (utero-salpingography) Note uterus unicornis Obstruction of the abdominal ostium prevents the passage of the injection fluid.
(Courtesy of Dr A Pinto Viégas)



Sterility due to blockage of the oviducts. Note that X-ray opaque fluid completely fills the uterine cavity, which appears to be normal the distal parts of both tubes are obstructed so that free passage of spermia and ova is impossible.
(Courtesy of Dr A Pinto Viegas)

matory or neoplastic lesions in the pelvis; congenital anomalies in the development of the sexual organs, etc.

X-RAY EXAMINATION often helps to detect tumors in the ovarian, suprarenal or hypophyseal region. The patency of the oviduct can be examined by two commonly used technics. In the *tubal insufflation method* (*Rubin*, 1920) carbon dioxide is passed through the uterus into the tubes and the peritoneal cavity, the resulting pneumo-peritoneum can be demonstrated by X-ray examination or by subjective symptoms (shoulder pain, etc.). Furthermore, the pressure in the insufflation apparatus rises only slightly if the tubes are patent, but reaches very high levels if they are closed. The passage of air can also be detected, by its characteristic sound, if a stethoscope is applied to the lower abdomen *Hysterosalpingography*, after injection of iodized oil and other X-ray opaque substances, may give further details concerning the exact position and permeability of the tubes.

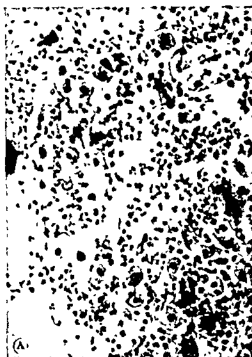
Examination of ENDOMETRIAL BIOPSIES and the VAGINAL SMEARS is of the greatest value in detecting ovarian diseases, since the histologic appearance of the uterine and vaginal mucosae exhibit characteristic changes under the influence of folliculoid and luteoid hormones respectively.

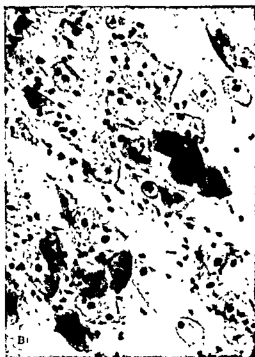
BIOCHEMICAL STUDIES, such as the B.M.R., blood and urine sugar and hemoglobin determinations are particularly valuable if changes in thyroid function, diabetes, anemia and other systemic diseases are suspected.

Among the HORMONE DETERMINATIONS, the urinary excretion of folliculoids, pregnanediol (as an indication of progesterone production), 17-KS and gonadotrophins are especially



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Atrophic vaginal
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(Courtesy of Dr E Shorr)

instructive. In all these determinations, it is advisable to obtain excretion curves extending over a whole or even several cycles, since single determinations are of comparatively little value.

THERAPY

In connection with the HORMONAL THERAPY of ovarian diseases, the folliculoid, luteoid, gonadotrophic, thyroid and perhaps also the testoid preparations are useful. The pertinent pharmacologic problems (dosage, route of application, sensitization by combined treatment with several hormones, etc.) have been reviewed in connection with the pharmacology of the individual hormones. For the therapy of well-characterized specific ovarian diseases, the reader is referred to the chapters dealing with these in particular (e.g., Metropathia Hemorrhagica, Ovarian Tumors). We shall limit ourselves, here, to the discussion of a few general principles, applicable to the therapy of a variety of ovarian diseases.

Hypogonadism. — In the treatment of hypogonadism and amenorrhea it is usually best to imitate the normal, sexual cycle by the successive administration of folliculoids during 18 days, and luteoids during the subsequent 8 day period. If, at the end of this time, hormone treatment is interrupted for a few days, true menstrual bleeding occurs from a progestationally prepared endometrium. This therapy also helps to develop the accessory sex organs (breasts, uterus, vagina) and to improve the otherwise subnormal libido.

A simpler and apparently equally effective procedure is the "2 day treatment" (*Zondek*), in which bleeding ensues 4 days following simultaneous intragluteal injection of 2.5 mg. of estradiol benzoate and 12 5 mg of progesterone on two consecutive days Of course, it will be realized that in the absence of ovulation, treatment with ovarian hormones can not restore fertility. Yet, in certain instances where hypogonadism is not due to complete destruction of the ovaries, such treatment re-initiates spontaneous ovarian and menstrual cycles.

Some gynecologists limit treatment to 8-14 daily doses of a folliculoid compound (e.g., 0.5-1 mg. of stilbestrol, or 30 mg. of estrone sulfate per os daily), or to luteoids alone (50 mg. of progesterone, divided in 5 injections of 10 mg. each on 5 successive days), a procedure which is usually followed by uterine bleeding 60 hours after the last injection in cases of secondary amenorrhea On theoretic grounds, the sequential administration of folliculoids and luteoids appears preferable, since it imitates natural conditions, but satisfactory results are sometimes obtained with folliculoids or luteoids administered singly If the amenorrhea is primary, and the endometrium entirely unprepared by endogenous folliculoids, pretreatment for about 5 days with a folliculoid, in the usual doses is essential

It should be kept in mind that as far as we know, absence of menstrual bleeding is not harmful in itself. Its artificial induction in an amenorrheic woman is chiefly of psychologic value unless ovulation is produced Hence the importance of producing a progestational endometrium is somewhat dubious.

In order to stimulate the ovary itself, GONADOTROPHIC PREPARATIONS must be administered. A variety of hypophyseal, urinary, and pregnant mare serum gonadotrophins, as well as combinations of the above, are commercially available. Some gynecologists recommend the use of gonadotrophins in combination with folliculoids, for the treatment of hypogonadism and amenorrhea Unfortunately, the commercial preparations of gonadotrophins are still impure, and unlike in experimental animals, it is rarely possible to produce

ovulation and thus to restore fertility with the gonadotrophins now on the market. We are as yet unable to lay down definite rules concerning the choice of the preparations and the clinician usually has to determine by trial and error which patient responds better to ovarian and which to gonadotrophic substances If the ovary is completely destroyed, it is of course useless to administer gonadotrophins.

In view of the frequent occurrence of hypogonadism in the presence of, sometimes latent, hypothyroidism, the administration of small doses of DESICCATED THYROID (½ to ¾ grains daily) is often advantageous. Indeed, it is claimed that such therapy may help even if there are no signs of hypothyroidism.

PROSTIGMINE has been recommended in the treatment of retarded menstrual bleeding It apparently produces pelvic hyperemia through its action upon the parasympathetic nervous system. It should be recalled that the folliculoids have been claimed to produce hyperemia through the release of acetylcholine, whose destruction is impeded by prostigmine. The applicability of this therapy is rather limited.

It is important to remember that the general condition of the patient plays a prominent rôle in the causation of many types of amenorrhea. Hence, a properly balanced DIET is recommended, particularly the control of excessive obesity, and in the event of anemia, IRON preparations. Light X-RAY treatment of the ovary or hypophysis have often been claimed to be beneficial in certain types of amenorrhea because of their alleged gonad-stimulating effect

The THERAPY OF OLIGO- AND HYPOMENORRHEA is based essentially on the same principles as that of other types of hypogonadism.

Hyperfolliculoidism. — For therapy see Hyperfolliculoidism on page 431

Hyperluteoidism. — For therapy see: Corpus Luteum Cysts and Hyperluteoidism on page 436

Dysmenorrhea. — The therapy of dysmenorrhea is still almost entirely empirical. In some cases, SURGICAL intervention is indicated if the cause is obstruction of the genital passages, endometriosis or malposition of the uterus. In certain instances, dilatation of the cervix with curettage proves beneficial. In very resistant cases, sympathectomy or hysterectomy is recommended, but the latter must, of course, be performed only on patients refractory to all other types of therapy

When excessive emotional reactions to the normal menses are the cause of dysmenorrhea, PSYCHOTHERAPY often gives excellent results

Recently, HORMONE THERAPY has become increasingly more popular and favorable results have been reported after treatment with large doses of folliculoids (which prevent ovulation), or small doses of testoids (which in addition to inhibiting ovulation, cause involution of the uterus). Gonadotrophic preparations and progesterone have also been recommended, the latter because it was believed to inhibit tonic uterine contractions

For the treatment of the pain itself, various SEDATIVES (salicylates, bromides and, in severe cases, morphine) may have to be prescribed.

Hypermenorrhea (or Menorrhagia). — In women with menorrhagias testoid treatment tends to diminish uterine bleeding because of the resulting atrophy of the endometrium In some instances, gonadotrophins or progesterone prove effective in diminishing the flow, although the mechanism of their action is not yet quite clear. Thyroid treatment is indicated in hypothyroid women In young women, temporary, in older, premenopausal women permanent X-ray or radium castration or even ovariectomy is recommended,

since it eliminates ovarian hormone production: but this should only be used as a last resource. In young women in whom the bleeding is very severe and irresponsive to all other therapeutic measures, hysterectomy without ovariectomy may be preferable.

Intermenstrual Bleeding. — Unless it is severe, this condition does not necessarily require any therapy. Curettage in itself may bring about a cure. In some cases, testoid or folliculoid hormones prove effective when given prior to the expected intermenstrual bleeding.

Chronic Cystic Mastitis. — This condition is very resistant to any form of therapy. Treatment with folliculoids and testoids has been recommended on the basis of rather doubtful hypothetic considerations. Both folliculoids and testoids stimulate mammary growth, and hence they are not likely to be beneficial unless their suppressing effect upon the endogenous hormone production of the ovary overcompensates for their direct breast-stimulating action. On the other hand, folliculoid therapy is often highly effective in the treatment of underdeveloped breasts

Vaginitis. — Gonorrheal vulvovaginitis in children and senile vaginitis in old women, respond very well to folliculoid therapy, and in such instances topical application in the form of vaginal suppositories is recommended

Sterility and Infertility. — Many cases of sterility are due to vaginitis, cervicitis, pelvic inflammation, stenosis of the cervix, displacement of the uterus, fibromyomas, systemic diseases such as anemia, diabetes, etc., or malnutrition In these instances, THERAPY SHOULD BE DIRECTED AGAINST THE SPECIFIC CAUSATIVE FACTOR. It must also be kept in mind that some women are constitutionally less fertile than others and that the fertility of the male partner must be ascertained before the blame is placed upon the woman. It is likewise well to explain to the patient that INTERCOURSE DURING THE MIDMENSTRUAL PERIOD (at the time of ovulation), is most likely to bring about pregnancy, after several days of abstention. The optimal time for conception can be determined by vaginal smears or basal body-temperature measurements. (See: "Estrus and Menstruation.")

ARTIFICIAL INSEMINATION with semen from a man of proven fertility is undoubtedly effective in cases in which the male partner is at fault. The procedure has been much criticized, however, both on moral and legal grounds.

As regards the endocrine therapy of sterility, THYROID preparations have often been claimed to be helpful, even in cases without any definite evidence of hypothyroidism. It is somewhat difficult to understand, however, why this measure is effective.

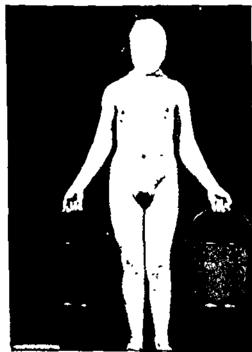
On theoretic grounds, treatment with GONADOTROPHINS would appear to be most logical, since these so readily produce ovulation in laboratory animals. As we have stated elsewhere, however, the gonadotrophins now available rarely, if ever, cause ovulation in primates. Correspondingly, results with various FSH and LH preparations or combinations of the two have not been very satisfactory in women.

Treatment with FOLLICULOID or LUTEOID preparations is advisable only if there is clinical evidence (biopsy, bioassay) of a deficiency in the endogenous production of these hormones In such cases, therapy should be adjusted to compensate for the functional deficiency, folliculoids being given during the first, luteoids during the second half of the cycle

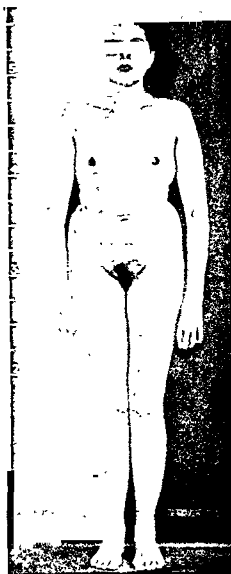
SPECIAL DISEASES OF THE OVARY

MALFORMATIONS AND ANOMALIES

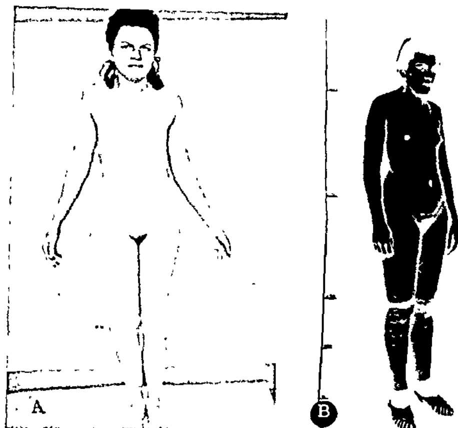
Aplasia (or Agenesis). — Very few cases have been reported in which both ovaries were absent at autopsy in women in whom there had been no reason to suspect a secondary destruction of the gonads during embryonic or postembryonic life. True ovarian agenesis is usually accompanied by manifestations variously described as TURNER'S SYNDROME or ALBRIGHT'S SYNDROME. This is characterized by great shortness of stature ("ovarian dwarfism"): infantile development of the mammary glands, uterus and vagina; diffuse osteoporosis; increase in the urinary elimination of gonadotrophins; diminution, but not complete absence, of axillary and pubic hair; and various congenital anomalies (e.g., coarctation of the aorta, cubitus valgus, scoliosis, absence of upper lateral incisor teeth and webbing of the neck).



Turner's syndrome (Ovarian agenesis)
Age 14 years. Webbing of neck is hardly noticeable because of plastic operation. Note increased carrying angle of arms, lack of breast development and moderate amount of pubic hair
(After F Albright et al Am J Med Sc 204, 625, 1942)



Primary Hypoovarianism. Age 26 years, primary amenorrhea, excessively long arms and legs, lack of breast and uterine development (uterine canal 4 cm in length), endometrium immature with no signs of progestational proliferation, vaginal smears of castrate type, skeletal maturity less than corresponding to 21 years of age Note immaturity of facial expression, sella normal as judged by X-rays, visual fields show no abnormality.
(Courtesy of Dr. E P McCullagh)



Ovarian agenesis. — A. Girl with primary amenorrhea, absence of breast development and shortness of the neck. Cubitus valgus not very marked. — B. Same patient after 4 months of intensive folliculoid therapy. Note increase in pubic hair and breast development, with prominent pigmented nipples. (Courtesy of Dr. E.-B. del Castillo.)

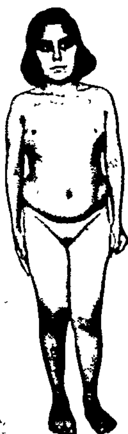
The frequent accompanying mental retardation may be due to congenital defects in brain formation.

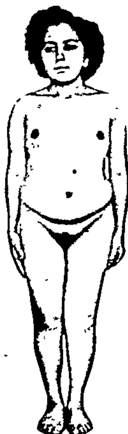
It is often difficult to differentiate these women from pituitary dwarfs, but unlike the latter, the ovarian dwarf exhibits an only slightly retarded bone age, a normal insulin tolerance curve, and an increased urinary FSH excretion. Furthermore, the ovarian dwarf responds to folliculoid therapy with marked axillary and pubic hair development while the pituitary dwarf does not. In some women, ovarian agenesis is accompanied by signs of virilism, especially hirsutism.

Hypoplasia of the Ovaries. — Primary hypoplasia of the ovaries is presumably a very rare condition. In allegedly pertinent cases, it is almost impossible to determine whether we are dealing with a true malformation of the gonad, with the result of pituitary malfunction, or with originally normal ovaries which underwent secondary involution under the influence of local damage.

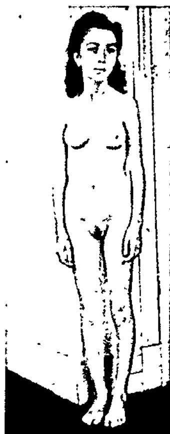
Clinically, this condition does not differ significantly from other types of severe hypoovarianism which, having commenced at a very early age is accompanied by primary underdevelopment of the accessory sex organs.

Accessory Ovaries. — Women with more than two ovaries are exceptional. Sometimes parts of an otherwise normal ovary are partially separated from the main gland and if this malformation goes further, certain portions of the gonad may become completely separated. These are usually referred to as SUPERNUMERARY or FALSE ACCESSORY ovaries. In exceptional instances, the additional ovary is fully equivalent —



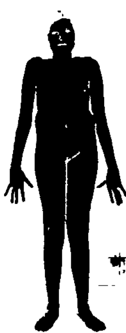


Ovarian dwarfism. — A 17-year-old girl with retarded growth and [illegible]



Hypoovarianism. 17-year-old girl with primary amenorrhea and scarce pubic hair Note that breast can be normal in severe hypogonadism (Courtesy of Dr J.-I. Lobo)





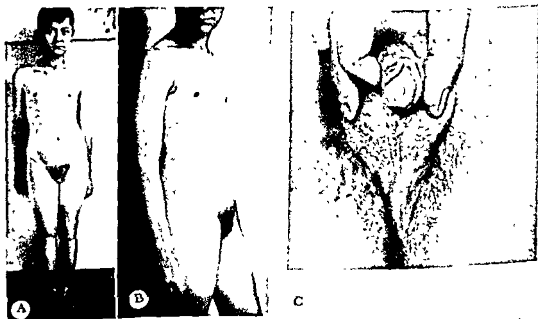


Primary hypoovarianism. 19-year-old girl with absence of pubic hair and breast development Note disproportionately long extremities and fingers open junction cartilage lack of pigmentation in areolæ and short neck (Courtesy of Dr E.-K. Shelton)

in size and function — to the normal gonads, indeed it may be connected with a third oviduct. In these cases, we speak of TRUE ACCESSORY OVARIES OR THIRD OVARIES. A surprisingly large number of these rare third ovaries become the site of tumor formation (mostly teratoids). This may be interpreted as indicating that congenital ovarian malformations result in a predisposition to tumor formation. It must also be kept in mind that the torsion of tumor-bearing ovaries with subsequent self-amputation and reimplantation may be confused with tumor-formation in ectopic ovaries.

Hyperplasia and Hypertrophy. — It is doubtful whether true hyperplasia of the ovaries ever occurs as a primary malformation. Probably most, if not all cases described by such terms as "the giant ovary" and "the large ovary" are actually due to chronic proliferative inflammatory processes, or to increased gonadotrophin production, rather than to a true congenital malformation. As with several other endocrine glands, it is impossible to distinguish between hyperplasia and hypertrophy due to causes inherent in the ovary itself, and corresponding changes resulting from increased pituitary trophic hormone production.

Primary Ectopia of the Ovary. — The malpositions of the ovary may be subdivided into two groups: (1) *primary ovarian ectopia* in which the ovary is abnormally situated, due to a disturbance in its embryonic development (usually incomplete descent during fetal life); (2) *secondary ovarian ectopia* comprising acquired malpositions, due to displacement of the gonads by growths, hernias of the ovary, etc. The distinction between these two groups is not always clear; for instance, inguinal hernias of the ovary are possible only if closure of the inguinal canal fails to occur during fetal life. In such instances, it is difficult to prove whether the malposition of the ovary itself is primary or secondary. Furthermore,



Pseudohermaphroditism. — A, B and C. Patient with pseudohermaphroditism, whose sex has not been verified by biopsy. Note unusually large clitoris or penis (3 cm in length), female pubic hair distribution. The testes were not palpable, the urethral orifice was about 2 cm below the penis-like organ. Rectal palpation revealed neither prostate nor testes or female accessory sex organs. The 9-year-old individual was mentally retarded and possessed a small palpable goiter. (Courtesy of Dr A. Pinto Vilgas.)

ovarian torsion may lead to spontaneous amputation of the gonad, with secondary reimplantation in other parts of the abdomen. [See also : Hernia and Prolapse (Secondary Ectopia) of the Ovary on p. 406.]

Ambisexuality (Hermaphroditism and Pseudohermaphroditism). — We use the generic term "AMBISEXUALITY" to designate the condition of individuals possessing both male and female characteristics. As outlined elsewhere in this book, even the normal human individual is somewhat ambisexual. Both folliculoid and testoid compounds are produced by men and women and even certain purified steroids (e.g., testosterone) exhibit both folliculoid and testoid activity. For the purpose of the present discussion however, the expression "ambisexuality" will be used as a generic term, designating individuals in whom the simultaneous presence of the characteristics of both sexes is exaggerated. Hence it includes not only cases in which the disturbance is due to a congenital malformation (hermaphroditism), but also tumors or hyperplasia of endocrine glands developing during postnatal life (for a more detailed discussion of these, see. "Adrenogenital Syndrome," "Arrhenoblastomas," "Cushing's Disease," "Testoid Hyperthecosis," "Lipid Cell Tumors of the Ovary," "Diseases of the Testis," etc.).

The term "TRUE HERMAPHRODITISM" (HERMAPHRODITISMUS VERUS) is used to designate the condition of individuals possessing both male and female gonadal elements Even this condition is normal, at least in some lower animals. Thus, many invertebrates are physiologically hermaphrodites inasmuch as every individual produces male and female gametes either at different times or synchronously. Some species are even self-fertilizing. Among vertebrates however, there are only few examples of true permanent hermaphroditism under normal conditions (see below).

In the early literature, there was a great tendency to develop complex systems for the CLASSIFICATION OF THE VARIOUS TYPES OF AMBISEXUALITY. It is amusing to note, for instance, that at a time when the medical literature knew only of 7 or 8 proven cases of true hermaphroditism, *Klebs* (1876) devised a system of classification and terminology in which 16 categories of true hermaphroditism were distinguished, merely because they were theoretically possible. Such systems played a great rôle in the medical literature, but they are hardly justified, since neither the intensity nor the extent (number of organs affected) of the hermaphroditic changes fall into natural, well-defined categories.

Young (1937) proposed the following simplified classification of true hermaphroditism as being closely in agreement with general usage :

(1) *Lateral hermaphroditismus verus* (An ovary on one side and a testicle on the other).

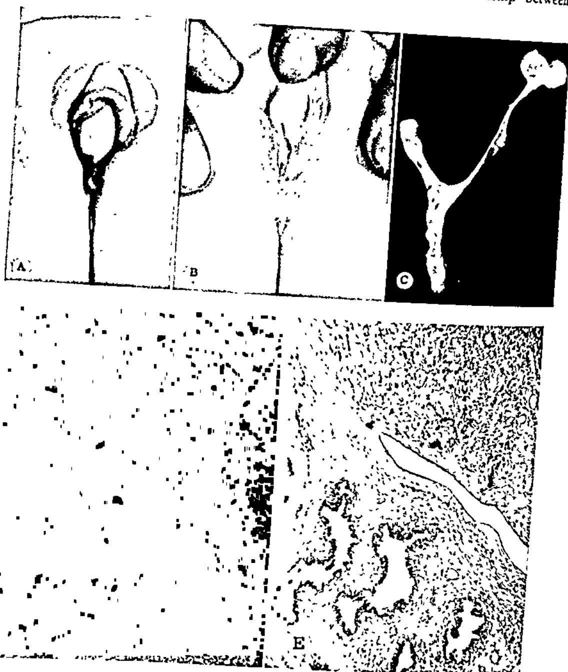
(2) *Unilateral hermaphroditismus verus* (Both ovary and testis on one side and one of the two on the other).

(3) *Bilateral hermaphroditismus verus* (An ovary and a testis on both sides).

In man, cases of true hermaphroditism are extremely rare. A careful study of the relevant literature revealed only 38 cases which in my opinion may be accepted as belonging to this category In one family, benign testicular tubular adenomas were observed in two hermaphroditic sisters (*Novak*, 1943). There were several additional "intersexual" individuals in the same family and the malformation was considered to be hereditary The gonads were described as "ovotestes"

The testes of true hermaphrodites do not tend to descend into the scrotum but remain in the abdomen or the inguinal canal Since spermatogenesis is inhibited even in otherwise normal

ectopic testes (see · Cryptorchidism), it is in accordance with expectations that ovotestes usually contain under-developed tubules, similar to those of ovarian tubular adenomas. This illustrates the close relationship between



True hermaphrodite. — A. Close-up of genitals showing phallus in position of clitoris surrounded by prepuce representing labia minora Labia majora showing corrugations reminiscent of scrotum — B. Close-up of genitals revealing phallus with urethra occupying position of clitoris. Beneath this is vaginal orifice — C. Gross specimen of pelvic organs showing uterus tube and bilateral ovo-testis — D. Microscopic section showing primordial ovarian follicles and seminiferous tubules in the same organ — E. Microscopic section showing presence of early-prostate-like tissue and primordial ovarian follicles in the ovo-testis of the opposite side

(Courtesy of Dr R C Grauer)

true hermaphroditism and virilization due to ovarian tumors.

In some instances however, both gonads consisted of comparatively normal ovarian and testicular tissue, while in others separate testes and ovaries were noted. In one individual only one of the gonads was examined by biopsy and proven to be an ovary, yet the patient had frequent intercourse with women and since living spermatozoa could be detected in the spermatic fluid, it is evident that the remaining gonad must have been a testis.

The term "PSEUDOHERMAPHRODITISM" (PSEUDOHERMAPHRODITISMUS) is used to designate the condition of individuals possessing either ovaries or testes, but both male and female secondary sex organs.

The classification of pseudohermaphroditism according to *Klebs* (1876), although extremely complex, is still so generally in use that we must mention it here. It distinguishes

(1) *Pseudohermaphroditismus masculinus externus.* (The sex glands and inner secondary sex organs are female, while the external genitalia are male).

(2) *Pseudohermaphroditismus femininus externus.* (The sex glands and inner secondary sex organs are male, but the external genitalia are female).

(3) *Pseudohermaphroditismus masculinus internus.* (The sex glands are male, but oviducts, uterus and vagina are also developed).

(4) *Pseudohermaphroditismus femininus internus.* (The gonads are female, but both male and female sexual passages are developed).

(5) *Pseudohermaphroditismus completus masculinus* (The sex glands are male, but all secondary sex organs are female).

(6) *Pseudohermaphroditismus completus femininus* (The sex glands are female, but all secondary sex organs are male).

In itself, the term pseudohermaphroditism is incomplete, unless modified by two of the following five adjectives, namely masculine or feminine and internal, external or complete. The first two designate the gonad, the last three the manner in which the genital structures differ from the sex of the gonads. By the use of these adjectives, all possible combinations can be designated fairly accurately (*Creevy*). These considerations led to the following modification of Klebs' classification ·

Pseudohermaphroditism

Designation	Gonads	Internal Sex Organs	External Sex Organs
Feminine External	Ovaries	Tubes and uterus present either normal or hypoplastic	To some extent, resemble those of the male
Feminine Internal	Ovaries	Tubes and uterus present Vestigial male structures present	Appear normal
Feminine Complete	Ovaries	Tubes and uterus absent or vestigial Vestigial male structures present	May appear to be completely masculine Well developed phallus with a urethra Labia closed to form a scrotum, etc
Masculine External	Testes	Normal and masculine	Hypospadias, cleft scrotum etc
Masculine Internal	Testes	Tubes, uterus present	Appear normal
Masculine Complete	Testes	Masculine organs absent or vestigial, tubes, uterus present	Almost entirely feminine

Most external and complete pseudohermaphrodites are reared as the wrong sex and when they marry, usually marry a member of the same sex.

Pseudohermaphroditism is much more common in females than in males and statistics indicate that about one out of every thousand women is pseudohermaphroditic. In many of these, the histologic structure of the ovary is approximately normal, while in others, excessive proliferation of the "male elements" in the hilum region (medullary cords, ovarian Leydig cells) or of heavily luteinized and sometimes cystic theca-cell nests (testoid hyperthecosis) account for the virilization.

The secondary sex organs of female pseudohermaphrodites show varying degrees of masculinization, such as development of a rudimentary prostate, hirsutism, a male type of skeleton, voice, libido and fat distribution. In male pseudohermaphrodites, cryptorchidism, hypospadias with hypoplasia of the penis and feminization of voice, libido and fat distribution are most striking

HOMOSEXUALITY may be regarded as a psychic type of pseudohermaphroditism, but since this condition is not necessarily associated with any definite change in ovarian structure, it will not be discussed here.

The term "INTERSEX" has been used by *Goldschmidt* (1931) to designate animals which originally developed as pure genetic males or females, but then changed in the direction of the opposite sex. In such individuals there is an intermediate period in which characteristics of both sexes are manifest

The term "GYNANDROMORPH" is often used to designate animals in which both the gonad and the secondary sex organs are male on one side and female on the other. This term may also be employed however for more complex types of ambisexuality, such as true hermaphroditism "due to a mosaic of genetically male and female cells" (*Witschi*, 1939)

Since neither intersexuality nor gynandromorphism have been definitely proven to exist in mammals, we shall not discuss them here.

Rare Malformations and Anomalies of the Ovaries. — The terms "ovarium lobatum," "gyratum," "succenturiatum," "bipartitum" and "disjunctum" are often applied to gonads with deep furrows in which part of the parenchyme is more or less completely separated from the rest. Some of these anomalies are obviously congenital, while others may be acquired during postnatal life.

"ECTROPION" OR PROLAPSE OF THE CORPUS LUTEUM (very rare) results from an eversion of the granulosa through the rupture point of the follicle at the time of ovulation. Thus, the resulting corpus luteum undergoes a prolapse which places the originally innermost layers of the granulosa to the outside. It will be recalled that in certain animals (e.g., elephantulus), this eversion occurs normally.

SPONTANEOUS AMPUTATION of the ovary is seen almost only in tumor-bearing gonads. The amputated ovary may reimplant itself in an ectopic position or remain floating in the peritoneum and become necrotic or even calcified.

The CORPUS LUTEUM LIBERUM (very rare) is a yellow body, which has become entirely separated from the ovary (presumably due to trauma or pressure from pelvic tumors). It may remain a free body in the peritoneum or reimplant itself in an ectopic position

HERNIA AND PROLAPSE (SECONDARY ECTOPIA) OF THE OVARY

The most frequent types of secondary ovarian ectopia are the hernia and especially one of its varieties, the prolapse The HERNIA may be defined as a transposition of the ovary from the abdominal cavity into a pouch covered by peritoneum. Because of its comparative frequency and its peculiar anatomic

characteristics, ovarian PROLAPSE deserves special attention. It is a transposition of the ovary into the posterior cul-de-sac where — depending upon the degree of prolapse — the ovary may or may not actually protrude into the vaginal lumen within a special peritoneal sac. Hence, a prolapse may merely represent a slight intraperitoneal transposition or a true vaginal hernia of the ovary.

The different sites of ovarian hernias are, in decreasing order of frequency: inguinal, femoral, sciatic, obturator, perineal, vaginal, umbilical, lumbar, broad ligament and abdominal scar.

From the endocrinologic point of view, herniation of the ovary is important because it is frequently accompanied by cystic degeneration or tumor formation in the gonad. It must be kept in mind that inguinal hernias can only occur in the case of a delayed occlusion of the inguinal canal and an exaggerated descent of the gonad Both of these changes are "male" characteristics (typical of testis development), and hence, inguinal hernias may be regarded in a sense as due to partial pseudohermaphroditism. They are not uncommonly accompanied by other signs of virilism and in many instances of true hermaphroditism, the ovotestes remain permanently in an inguinal location.

Frequently, the herniated ovary continues to function normally although it may cause discomfort and local pain at the time of ovulation and menstruation In the case of vaginal prolapse, it tends to produce severe dyspareunia.

The most serious COMPLICATIONS of ovarian hernias are due to strangulation and torsion of the pedicle.

The THERAPY is replacement of the ovary into its normal position, if possible. Often however, it is preferable to perform an ovariectomy, especially if the gonad is cystic or inflamed

TORSION OF THE OVARY

Because of the comparatively great *mobility of the ovaries, they are rather* subject to *torsion* at the pedicle. This may lead to severe nutritional disturbances in the gonads and even necrosis or self-amputation. Torsion occurs most frequently in tumor-bearing ovaries which have elongated, narrow pedicles. Pregnancy is an important predisposing factor. Perhaps the development of a large corpus luteum and the gradual enlargement of the uterus help to displace the ovaries during gestation.

CLINICALLY, the predominant symptoms are those of sudden intense pain in the lower abdomen with accelerated pulse and often severe shock. The most frequently made diagnostic errors are due to confusion of ovarian torsion with acute appendicitis, or ectopic pregnancy.

The TREATMENT of choice is the surgical removal of the twisted ovaries.

RETROGRESSIVE CHANGES

The retrogressive changes of the ovary are of no great endocrinologic importance Among them, it suffices merely to mention COLLOID or HYALINE DEGENERATION and AMYLOIDOSIS, which are very rare

Simple ATROPHY is almost invariably due to deficient gonadotrophin formation, while CIRRHOSIS is most commonly a result of chronic inflammation or cystic degeneration.

NECROSIS is almost always due to torsion, tumors, self-amputation and other diseases conducive to nutritional disturbances in the ovary.

CALCIFICATION and even OSSIFICATION may occur in the ovary during the healing of inflammatory or degenerative lesions These are often detectable by X-ray examination

VASCULAR DISTURBANCES

Ovarian HEMORRHAGES are of great clinical importance because of their comparative frequency and the serious clinical manifestations which they may elicit. Usually, they are due to excessive bleeding from a ruptured follicle, a corpus luteum or an ovarian tumor. The incidence of ovarian hemorrhage is estimated to be about 1% among all gynecologic and surgical laparotomies. They occur more frequently during the menarche, and usually at the time of ovulation. Corpus luteum hemorrhages are often seen during pregnancy and the increased pelvic hyperemia and intra-abdominal pressure of gestation also predispose to hemorrhage from ovarian tumors.

The main *clinical* characteristics in the typical case are midmenstrual pain, slight elevation of the temperature, some polymorphonuclear leukocytosis and — in the case of severe hemorrhages into the peritoneum with considerable loss of blood — a weak pulse with signs of severe shock

In many instances, no therapy is necessary, since the bleeding stops spontaneously If shock is present, blood transfusion and external application of heat are advisable after the operation. The simplest surgical procedure is to strip the hematoma cavity of its lining and approximate its walls with a fine catgut suture. If the ovary is severely damaged, complete resection may be necessary

Because of the large number and comparatively great width of the veins in the ovarian hilum region, they are rather subject to VARICOSITY (varicocele), especially if circulation is impeded as in retrodisplacement or subinvolution of the uterus Usually varicocele causes no endocrine derangement and in most cases it can be cured by ligature and removal of the varicose veins

INFLAMMATIONS

Inflammations of the ovaries are rarely of endocrinologic significance, except in differential diagnosis. With regard to their COURSE, we distinguish acute and chronic oophoritis; with regard to the LOCALIZATION of the inflammatory reaction, it is customary to delimit diffuse, interstitial oöphoritis from abscess formation in the cavities of follicles, corpora lutea or ovarian cysts.

Concerning the PORTAL OF INFECTION, it is known that microbial invasion of the ovary may be *hematogenous*, through the *lymphatics*, or by ascension, through the *Fallopian tubes*. Most frequently, the infection spreads by direct *contiguity* and leads to simultaneous development of oöphoritis in combination with salpingitis. Sometimes, oophoritis is due to infection by contiguity from an inflamed appendix. Gonorrheal infection tends to spread through the tubes, while streptococcus infection shows a predilection for propagation through the parametria, probably because it occurs most frequently postpartum or after abortion when the uterus is traumatized

As regards the ETIOLOGIC microörganism, the *gonococcus*, *streptococcus* and *tubercle bacillus* are of the greatest importance, though *syphilis*, *staphylococcus* and many other microbial infections may also lead to ovarian inflammation.

The microorganism of *mumps* is believed to possess a special affinity for ovarian tissue, thus causing oophoritis, comparable to the more common mumps-orchitis. Oophoritis is a more serious consequence of mumps than orchitis, since it leads to peritoneal irritation and hence may cause severe systemic manifestations

Oophoritis is a frequent cause of sterility, mainly because it leads to adhesions preventing the migration of ova.

but only rarely does it seriously interfere with the endocrine activity of the ovaries.

Pregnancy and the puerperium appear to predispose to ovarian inflammation. It has frequently been stated that various types of strain (e.g., physical work, cold baths, dancing, alcohol and sexual excesses) may cause oophoritis, especially if the patient is exposed to these stimuli during the menstrual period. This is mere superstition, since we have no proof that such agents could by themselves cause inflammation of the ovary. It is possible however, that they so decrease general resistance as to facilitate infection and subsequent inflammation.

DISEASES OF THE SEXUAL CYCLE

Definition. — For anomalies in the sexual rhythm (oligomenorrhea, polymenorrhea); the abnormalities in the quantity of the menstrual flow (hypomenorrhea, retention of menses, menorrhagia); as well as the phenomenon of midmenstrual bleeding, see : pages 385-398 in the previous chapter on Ovarian Diseases in General. Here we shall limit ourselves to the diseases of puberty, the menopause, the derangements of the normal correlation between ovulation and menstruation (in animals, estrus) and vicarious menstruation.

Diseases of the Pubertal Period. — *Irregularities of the sexual cycle often* occur during the first months or years after the menarche The most common among these are the so-called PUBERTY HEMORRHAGES. *They are usually due* to metropathia hemorrhagica, with excessive and prolonged bleeding, at irregular intervals, from a purely follicular type of endometrium. In most instances, the bleeding is probably not preceded by normal ovulation, but it is incorrect to refer to any uterine hemorrhage as "anovular," merely because progestational proliferation of the endometrium has not occurred It is quite conceivable that the follicle may rupture and the ovum be discharged, without there being subsequent luteinization of the granulosa with the formation of sufficient corpus luteum hormone to cause progestational uterine changes. In any event, the hemorrhages are due to a disturbance in the normal sequential production of folliculoids and luteoids. The endometrium tends to exhibit the characteristics of mild metropathia hemorrhagica, but occasionally signs of progestational proliferation are detectable in endometrial scrapings.

The condition is presumably not merely due to excess folliculoid hormone production in itself, since the bleeding usually ceases under the influence of treatment with folliculoids The hemorrhages are more probably the result of irregular fluctuations in folliculoid production and the absence of cyclic progesterone secretion The *intervals between flows may be shortened, prolonged or completely irregular.*

If the loss of blood is severe, hemostasis may have to be secured by *packing of the vagina or curettage* Administration of pitressin tannate in oil or ergot has also been found highly effective in some cases. In general, daily *administration of 6 mg. of stilbestrol,* 7.5 mg of estrone sulfate, or of other folliculoids in equivalent doses, stop the bleeding within a few days This treatment can be continued for 2 or 3 weeks, after which the discontinuation of therapy is followed by the usual withdrawal-bleeding In some cases the resulting hemorrhage is of alarming severity, but often several cycles of folliculoid therapy eventually restore normal periods Some gynecologists recommend cyclic progesterone administration Gonadotrophin therapy is not as consistently successful

It is well to realize that infrequent bleeding from a follicular-phase endometrium, or even occasional excessive loss of blood during adolescence, is no cause for grave concern; in most instances, these anomalies are readily amenable to the above-mentioned therapeutic measures and frequently they disappear spontaneously. More drastic *interventions, such as X-ray treatment or partial resection of the ovaries, are to be avoided.*

When *puberty* occurs before the 9th year of age, we speak of PRECOCIOUS PUBERTY, although this strict delimitation is perhaps somewhat arbitrary. It must be borne in mind that precocious menstruation or precocious development of accessory sex characteristics is not synonymous with precocious puberty. True precocious puberty is a rather rare condition in which normal, potentially fertile, ovarian cycles commence at an abnormally early age. This is accompanied by precocious development of the accessory sex organs and the soma *in general*

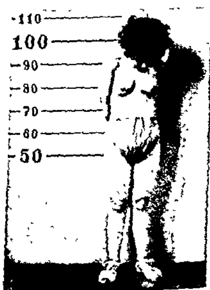
The term "*precocious pseudopuberty*" is used to designate diseases in which external manifestations of sexual maturity occur while the ovaries remain immature Folliculomas, adrenal-cortical hyperfunction, pineal and midbrain lesions may cause precocious pseudopuberty as described in other chapters of this book. In these, the uterine bleeding is usually irregular and accompanied by an excessive or heterosexual development of the accessory sex organs.

True precocious puberty may lead to the commencement of regular, cyclic menstruation even in girls below two years of age, who are healthy and normal except for the precocious assumption of the mature female form (breast growth, development of pubic and axillary hair, precocious ossification of the cartilaginous skeleton, widening of the pelvis etc.).

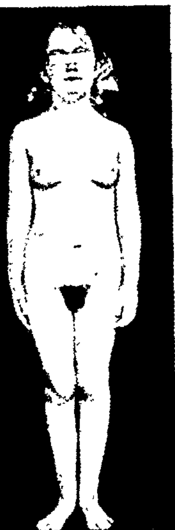
Although even precocious pseudopuberty (e.g., that due to granulosa cell tumors) may cause periodic menstrual bleeding from a purely follicular-phase endometrium, premature fertility occurs only with *true precocious puberty*. In such instances, pregnancy *may ensue at an extraordinarily early age* and several cases have been described in which girls of 5-12 years became pregnant, and subsequently delivered, normal children.

The primary cause of true precocious puberty is not known, but undoubtedly there must be a premature initiation of normal, cyclic gonadotrophin production, in order to *explain the formation of follicles, the discharge of ova and the subsequent corpus luteum formation.*

The so-called "overdevelopment-obesity syndrome" (early sexual maturity, obesity, advanced bone age, etc.) may also belong to this group.



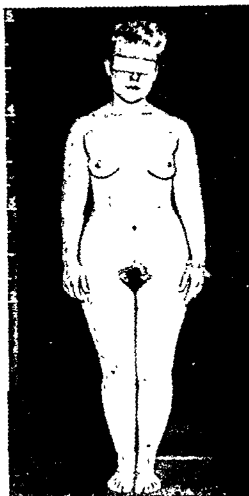
Precocious puberty. 4-year-old girl in whom breast development began at three years and soon afterwards uterine bleeding commenced and reappeared regularly in 27-day cycles There is pubic hair development and great precocity of ossification *Urinary* folliculoid elimination was high. The child became bashful and self-conscious Exploratory laparotomy *revealed a mature ovarian follicle* but no tumor Apparently this is a case of true precocious puberty (Courtesy of Dr J I Lobo)



Precocious puberty. Age 8 years. Encephalitis followed by epilepsy at age of 5 Breasts, axillary and pubic hair well developed, sella normal as judged by X-rays, visual fields normal bone age about 12 years, urinary FSH 26-53 MU /24 hrs
(*Courtesy of Dr E P McCullagh*)

In very young girls with precocious sexual development, exploratory laparotomy is usually justified, in order to determine the cause of the condition If the case is definitely identified as true precocious puberty, no radical therapy is necessary, but the child must be guarded against excessive self-consciousness and the possibility of sexual violations which are extraordinarily common in such girls, since their body is much more mature than their mind

It is rather generally, though somewhat arbitrarily, agreed that if the *menarche* is postponed until after the 17th year of age, we may speak of DELAYED PUBERTY. It must be kept in mind, however, that the absence of external signs of menstruation may be due merely to malformations of the genital passages; in that case, other signs of sexual maturation proceed normally and physical examination usually reveals the cause of retention of the menses.



Precocious puberty Age 15½ years, development of breasts axillary and pubic hair, vulva, vaginal *smears* and uterus of adult type Comparative shortness of limbs reminiscent of achondroplasia X-rays reveal no abnormality of sella Urogram gives no indication of adrenal tumor Bone-age about 21 years or more
(*Courtesy of Dr E P McCullagh*)



Precocious puberty due to cerebral lesion. 9-year-old girl with posterior cranium bifidum, hydrocephalus, precocious puberty and diabetes mellitus Menses appeared at the age of 8 years, breasts began to develop at 7 years Mental development greatly retarded, ataxia, B M R + 18%, bone age corresponding to approximately 12 years, ventriculogram shows marked enlargement of both lateral ventricles and third ventricle, sella is normal to X-ray FSH less than 13 M U /24 hrs

(Courtesy of Drs R W Schneider and E P McCullagh)

As previously mentioned, various climatic and dietary factors can retard sexual maturation; a delay in the onset of puberty may merely be one manifestation of the general-adaptation-syndrome to damaging agents. It is also noteworthy that obese individuals usually experience their menarche later than normal. Other common causes of delayed puberty are hypopituitarism, hypothyroidism or primary under-development of the ovaries themselves. In the latter case, we are usually dealing with primary amenorrhea, that is, normal puberty fails to occur at any time

A slight delay in the onset of menstruation requires no therapy, while the treatment of considerably delayed puberty is identical with that of primary amenorrhea (see : Ovarian Diseases in General).

Diseases of the Menopause. — The term MENOPAUSE (from the Greek: menos = month and pauein = to cease) is used to designate the cessation of menstrual cycles. Some investigators prefer the term "climacteric" (from the Greek : climakter = the rung of the ladder) which is defined as the entire period between regular menstruation and its complete cessation. The word "climacteric" is also applicable to the corresponding period in men when sexual functions gradually cease. The average normal menstrual life lasts 33 years and the menopause occurs in women between 45 and 50 years of age. In men, the climacteric is less well-defined and hence more difficult to delimit, but usually it occurs approximately at the same age as in women.

PREMATURE MENOPAUSE may result from surgical removal or destruction of the ovaries by X-rays, radium or local disease. Various debilitating diseases may cause cessation of menses through the repeatedly mentioned decrease in gonadotrophin production, resulting from the general-adaptation-syndrome Curiously, in the latter cases there are rarely any climacteric disturbances Hysterectomy brings about a cessation of menstruation but is not necessarily accompanied by immediate signs of ovarian deficiency. In some instances, premature menopause sets in without any obvious cause, often in women whose menarche occurred at an unusually early age, though sometimes there is early menarche with late menopause

and vice versa. In general, one does not speak of premature menopause unless the menses cease before the 35th year of age.

DELAYED MENOPAUSE is a condition in which normal menstrual cycles continue past the 55th year of age. This is an anomaly, but hardly a disease.

MENOPAUSAL DISTURBANCES are on the border-line of the normal. Certain derangements are manifest in every woman during this critical period of the "change of life," but their exaggeration may lead to severe pathologic conditions.

The *ovary undergoes involution after* the menopause, but there is no strict parallelism between the cessation of menstrual bleeding and that of ovulation. During the climacteric period monthly bleeding may continue, although ovulation has ceased (anovular *menstruation*). In other instances, ovulation appears to occur in the absence of menstruation (amenstrual ovulation). These derangements are identical with those described (p. 414) under the heading of "Derangements in the Correlation between Ovulation and Menstruation." Progestational transformation of the endometrium, and even pregnancy (a definite proof of ovulation) may ensue after the cessation of normal menses The discrepancies between ovulation and menstruation are probably due to the fact that during the climacteric, ovarian hormone production may be sufficient to cause uterine bleeding, even though ovulations do not occur and, vice versa, ovulation can continue when the production of ovarian hormones has declined to a level incompatible with normal menses

Extensive senile involution of the ovary does not occur until several years after the menopause.

The *uterine changes* of the menopausal period are particularly conspicuous Sometimes menstruation ceases abruptly, while at other times, several periods are missed, but menstruation recurs at irregular intervals. Frequently, the last periods of flow occur from a *follicular*-phase endometrium, because folliculoid hormone production continues after progesterone formation has ceased for some time. Eventually, however, both the endometrium and the musculature of the uterus involute as markedly as after complete castration.

The *vagina* atrophies, its lumen shrinks, the rugæ of the walls disappear, vaginal fluid is scanty and the mucosa becomes dry and glistening Microscopically, the vaginal mucosa is reduced to 4-5 layers of atrophic, nucleated cells containing no glycogen These changes predispose the mucosa to infection (senile vaginitis) and leukoplakia

The *urethra* may be involved in the vaginal atrophy and senile urethritis, incontinence or abnormal frequency of micturition may result.

The *oral mucosa* sometimes undergoes an atrophy similar to that of the vagina This predisposes to ulcerative stomatitis

The *breasts* become flaccid and pendulous, often due to resorption of fat, while the nipples decrease in size and lose their erectility At the same time, there is a tendency towards fibrosis of the breasts, with the formation of minute cysts due to dilatation of the milk ducts.

Severe *psychologic changes* (psychoses, involutional melancholia) are uncommon, but many women suffer from depression, headaches, digestive symptoms and numerous other subjective manifestations, some of which are undoubtedly caused by a sense of inferiority, resulting from the cessation of sexual functions Libido is largely preserved for several years and normal orgasm may be experienced after cessation of the menses

The most important manifestations of the menopause are the *vasomotor symptoms*, such as hot flushes involving the neck, head and upper part of the thorax, or less frequently, the entire

body. These are often accompanied by profuse sweating, which tends to follow immediately upon the flushes. The pathogenesis of the vasomotor phenomena is not yet clearly understood, but their immediate cause is certainly a deficiency in ovarian hormones, since similar manifestations can be evoked even at an earlier age by ovariectomy.

Signs of *virilization*, the so-called "menopausal virilism" (deepening of the voice, growth of facial hair, apical baldness, virilization of body contours and facial expression) are rather common among women of the climacteric age. They are probably due to a diminution of ovarian folliculoid formation and perhaps also to increased testoid production by the adrenal cortex.

Climacteric *arthritis* is likewise very prevalent. It usually begins as a chronic synovitis, but later, becomes indistinguishable from hypertrophic arthritis. Its pathogenesis is not known.

The most characteristic *hormonal derangements* during the natural or artificially-produced menopause are: (1) a great decrease in the urinary elimination of *folliculoids*, although traces of such hormones are detectable even several years after cessation of the menses; (2) a greatly increased urinary elimination of *gonadotrophins* (10-50 times the normal amount) with a measurable increase in the gonadotrophin content of the blood; (3) *Pregnanediol* elimination (probably of adrenal origin) may continue, in traces, several years after the menopause; (4) the *17-KS* and biologically-active *testoids* in the urine have been claimed to show a temporary increase, but this requires confirmation.

The comparatively common syndromes of mild *menopausal Cushing's syndrome* and *menopausal hyperthyroidism* indicate that the severe endocrine derangements of this critical period of life may involve a variety of glands of internal secretion in addition to the gonads themselves.

Most women need no *therapy* other than reassurance. In severe cases, folliculoid treatment is highly effective, especially in combatting the vasomotor disturbances and the profuse sweating. Control by vaginal smear is helpful in the evaluation of this treatment. The danger of producing tumors with folliculoids has probably been somewhat overrated. However, it is well to interrupt the treatment from time to time, not only in order to decrease the probability of producing neoplasms, but also to prevent the formation of a cystic hyperplastic endometrium.

Essentially the same therapy is used whether the disturbances are due to spontaneous or artificially-induced (ovariectomy or X-ray castration) menopause.

Derangements in the Correlation between Ovulation and Menstruation or Estrus. — Certain diseases of the sexual cycle are due to a derangement of the normal correlations between production of ova and ovarian hormone secretion. We speak of AMENSTRUAL OVULATION when the ovum is discharged, but uterine bleeding fails to occur, or arises from a follicular-phase endometrium. Sexual intercourse may lead to pregnancy, even in women who have been amenorrheic for a long time. This could be explained on the basis of amenstrual ovulation; there might be cases with sufficient progesterone production to permit implantation, but with a derangement in the normal cyclic withdrawal-bleeding. However, this etiology is difficult to prove; it is also possible that the act of sexual intercourse in itself has caused ovulation, although previously, in the absence of coitus, neither menstruation nor ovulation had occurred.

Corresponding derangements in animals lead to "anestrous ovulation."

whose occurrence is much better established by simultaneous histologic study of vaginal and ovarian changes.

ANOVULAR MENSTRUATION is a condition in which no ova are discharged from the ovaries, but true menstrual bleeding occurs from a progestational endometrium. In these cases, apparently the follicles mature and are transformed into active corpora lutea, but the ova remain enclosed in the follicular cavity due to some interference with their discharge ("atretic corpora lutea"). Such ova subsequently degenerate and cannot be fertilized. Some cases of ovarian pregnancy within corpora lutea indicate, however, that in exceptional instances, not-discharged ova can give rise to gestation.

It is incorrect to speak of "anovulatory cycles" when there is neither ovulation nor corpus luteum formation, since then there can be no menstrual cycle but only repeated uterine hemorrhages from a "follicular" endometrium.

Vicarious Menstruation. — We speak of vicarious menstruation when cyclic hemorrhages occur either simultaneously with, or instead of menstruation, from organs other than the uterus. The nasal, conjunctival and oral mucosæ; the intestines, ears and the mammary glands are sites of predilection for such hemorrhages. Here probably abnormal vasomotor phenomena are conducive to rupture of blood vessels. The alleged liberation of acetylcholine under the influence of folliculoids may have something to do with such a derangement.

The most common type of vicarious menstruation, however, is undoubtedly due to external endometriosis. The transplantation of endometrium onto the ovarian surface or other parts of the peritoneum, its invasion into the umbilicus and sometimes even the urinary passages, readily explains many instances of vicarious menstruation from such sites. The correctness of this interpretation has repeatedly been confirmed by the histologic demonstration of typical endometrial tissue at the site of the bleeding. (See : pp. 467-475.)

OVARIAN TUMORS IN GENERAL

DEFINITION

It is evident from our "definitions" of other endocrine gland tumors that a clear distinction between hyperplasia and tumor formation is always somewhat artificial This is particularly true of the ovarian neoplasms It has been said that " a tumor is an autonomous new growth of tissue" (*Ewing*); or that "a tumor proper is a mass of cells, tissues, or organs resembling those normally present, but arranged atypically. It grows at the expense of the organism, without, at the same time, subserving any useful function" (*Adami*).

There are several types of ovarian growths which are not true neoplasms in the usual sense of the word. Yet they represent tissue proliferations, which are comparatively autonomous and serve no useful purpose In the present state of our ignorance, the concept of tumorous growth — as that of any other of life's mysteries and even the concept of life itself — is embraced by experience and not by rational delimitation. Hence we shall not enter into a theoretic discussion of this problem, but will include in the present section a number of ovarian growths which have so many characteristics in common that they are best studied conjointly, for mere didactic reasons

Thus, we shall deal here with growths which are not considered to be true neoplasms (e g., follicle-retention cysts, corpus luteum cysts), merely because their clinical behavior and their ability to produce hormones make it expedient to review them together with corres-

ponding true ovarian neoplasms. Endometriosis of the ovary is also included in the present section, partly because in its morphology and clinical course it resembles the more orthodox ovarian growths, and partly because we are not yet convinced of its non-neoplastic nature. The extra-ovarian form of endometriosis is reviewed conjointly with the ovarian, in order to avoid duplication of data.

The salient characteristics of hyperfolliculoidism (such as is produced by follicle-retention cysts and folliculomas) and hyperluteoidism (such as is produced by corpus luteum cysts and corpus luteum tumors), will be considered here in detail conjointly with the causative ovarian growths, hence only cursory reference was made to them in connection with other ovarian diseases.

CLASSIFICATION

"Ovarian tumors present a wider scope of structure, greater individual variation and a more complex embryologic and histogenetic basis than those of any other organ, and for these reasons, they have escaped satisfactory classification" (*Ewing*).

The criteria upon which classifications have been based are MORPHOLOGIC (e.g., separation of cystic from solid, epithelial from mesenchymal tumors); EMBRYOLOGIC or HISTOGENETIC (e.g., *separation of growths originating from* the follicles, interstitial cells, ectopic tissue inclusions) and CLINICAL (e.g., separation of the benign from the malignant, or of hormone-producing from endocrinologically "silent" growths).

Unfortunately, no matter how we formulate our subdivisions, there are always so many intermediate groups and overlappings between different groups, that in most instances a tumor appears to fit into several groups with almost equal justification.

In this book, we shall classify the ovarian tumors according to a system which appears to be most satisfactory from the endocrinologist's point of view; *it is partly based on the morphologic structure, but mainly on the hormone-producing ability of the neoplasms*

PATHOLOGIC ANATOMY

The morphologic features of ovarian tumors are extremely diverse, since a variety of fundamentally different neoplasms may develop in the female gonad (see: sections dealing with specific tumor types). Their size varies from minute microscopic growths to the largest tumors ever seen in man. Sometimes the cystic tumors are heavier than the patient herself and ovarian neoplasms weighing up to 300 pounds have been recorded. These "mammoth tumors" immobilize the patient and may cause severe dyspnea, vascular disturbances (varicose veins, edema of the thighs, "caput medusæ") or prolapse of the uterus, merely because of their extraordinary size. Sometimes they are attached to the ovarian surface or the ligaments by long pedicles which permit the tumors to migrate from their original position towards Douglas' space, where they may become impacted, or towards the abdominal cavity, where there is more space for expansion.

Ovarian tumors are often bilateral. Originally benign neoplasms may undergo malignant transformation or degenerative changes such as liquefaction-necrosis, calcification, edema with hemorrhages, etc.

INCIDENCE

The GENERAL INCIDENCE of ovarian

3%.

The percentual incidence of the various types in a series of more than 1,000 ovarian tumor-bearers *(Bernstein)* was as follows:

	36
Follicle cysts	16
Dermoid cysts	14
Serous papillary cystadenocarcinomas	11
Corpus luteum cysts	6
Pseudomucinous papillary cyst-adenomas	4
Endometriosis of the ovary	3
Serous papillary cystadenomas	2 6
Tubo-ovarian cysts	2
Fibromas	

Pseudomucinous papillary cyst-adenocarcinomas	1
Solid medullary and undetermined carcinomas	1
Sarcomas	0.8
Malignant teratomas	0.7
Krukenberg tumors	0.5
Squamous carcinomas in dermoid cysts	0.2
Dysgerminomas	0.2
Carcinosarcomas	0.1

The AGE INCIDENCE of the various ovarian tumor types differs (see: each specific type), but about 40% of all ovarian tumors occur in women 30-40 years of age.

The PREGNANCY INCIDENCE among women, while under observation for various types of ovarian tumors, is estimated to be about 3.5%. Conversely, the ovarian tumor incidence among pregnant women is about 1% Many investigators believe that pregnancy predisposes to ovarian tumor formation, perhaps due to the pelvic hyperemia, the increased folliculoid hormone production or other metabolic changes accompanying gestation

PATHOGENESIS

The HISTOGENESIS of ovarian tumors has been touched upon in the chapter on the embryology of the ovaries, it will receive further attention in connection with the various specific tumor types

Little was known until recently about the FUNCTIONAL PATHOGENESIS of ovarian tumors, that is to say, the factors likely to promote tumor formation in the ovary Statistical studies suggest that *repeated* pregnancies and hereditary factors may have a predisposing effect Experimental findings indicate that ovarian neoplastic disease is related to a breakdown of the normal ovarian-hypophyseal relationship Follicular and luteal cysts, and hemorrhagic luteal cysts have been reported in animals after extensive partial ovariectomy (see p. 376) Recently, true ovarian neoplasms have been noted when the ovarian control of the hypophysis was deranged by intrasplenic ovarian grafting (see p 354) in castrates Here, the ovarian hormones pass through the liver before they reach the general circulation Hence the ovarian graft is over-stimulated by the uncontrolled hypophysis There is, in the rat, excessive luteinization of the enormously enlarged ovary, but also production of non-luteinized granulosa cell tumors (*Biskind et al*) In the guinea pig, cystic growth of mostly hemorrhagic follicles prevails, but later luteomas also develop (*Lipschutz*) In mice these tumors metastasize and are transplantable (*Li and Gardner, Furth and Sobel*) These tumors in rats and mice are similar to those which can be produced in mice by X-rays (see p 384)

CLINICAL COURSE

The clinical course of ovarian tumors in general — disregarding the symptoms of the various specific types — is mainly characterized by the manifestations due purely to the physical presence of a growth in the pelvis. The position and shape of the uterus and oviduct can be influenced by pressure or adhesions. Ascites can develop with practically any type of ovarian tumor and is estimated to be present in about 20% of all cases. It is particularly frequent with malignant neoplasms, papillomas and fibromas. Pleural fluid accumulations are present almost only with fibromas.

Mammary gland engorgement, sometimes with tenderness and lactation is rare among patients with ovarian tumors, except with hormone-producing neoplasms.

Fertility is not necessarily influenced even by large bilateral tumors, as long as an adequate amount of normal gonadal tissue remains.

COMPLICATIONS

The clinical course of ovarian tumors is very frequently altered by a variety of complications among which torsion of the pedicle, rupture of cystic tumors with massive hemorrhages, infection of the tumors (especially following perforation to the outside or into the intestinal tract), incarceration within the pelvis (usually due to immobilization by intraligamentous growths or adhesions), the development of hernias (due to increased intra-abdominal pressure), ectopic pregnancy, intestinal obstruction and circulatory disturbances are the most important.

Very large tumors may cause disturbances owing to vertical displacement of the heart, pressure upon the stomach or compression of the urinary bladder and ureters.

Table illustrating our classification of ovarian tumors
(After H. Selye: "Ovarian Tumors," Encyclopedia of Endocrinology, 1946.)

BENIGN		MALIGNANT	
POTENTIALLY ENDOCRINE NEOPLASMS		*POTENTIALLY ENDOCRINE NEOPLASMS*	
Follicle cysts (persistent follicles)		———	
Small cystic degeneration		———	
Folliculomas		*Malignant folliculomas* (granulosa cell carcinoma)	
Lipid cell tumors		*Malignant lipid cell tumors*	
Corpus luteum cysts, corpus luteum adenomas.		Corpus luteum carcinomas (and sarcomas ?)	
Leydig cell adenomas		Leydig cell carcinomas	
Adrenal rest adenomas		Malignant hypernephromas	
Testoid hyperthecosis		———	
Tubular adenomas (arrhenoblastomas)		*False Seminomas* (dysgerminomas)	
Thyroid tumors (struma ovarii)		———	
———		*Chorionepitheliomas* (Chorion carcinomas)	
NON-ENDOCRINE TUMORS		*NON-ENDOCRINE TUMORS*	
PREPONDERANTLY EPITHELIAL NEOPLASMS		PREPONDERANTLY EPITHELIAL NEOPLASMS	
Common Cysts		*Common Carcinomas*	
Serous	*Pseudomucinous*	*Serous*	*Pseudomucinous*
Macrocystic	Macrocystic	Primary solid carcinomas	———
Microcystic	Microcystic		
Tubular adenomas	Tubular adenomas	Carcinomatous serous cystomas	Carcinomatous pseudomucinous cystomas
Papillomas	Papillomas		
Racemose cystomas	Racemose cystomas		
Peritoneal papillomatosis	Pseudomyxoma peritonei	Metastatic serous carcinomas	Metastatic pseudomucinous carcinomas (including Krukenberg tumors)
(Mesonephromas)	———	(Malignant mesonephromas)	
———	(Brenner tumors)		
Dermoids and embryomas		*Solid teratomas* (carcinomatous or sarcomatous dermoids)	
Benign nerve tissue tumors		*Malignant nerve tissue tumors*	
NON-EPITHELIAL NEOPLASMS		NON-EPITHELIAL NEOPLASMS	
Fibromas		*Common sarcomas* (spindle and round cell)	
Myxomas		*Myxosarcomas*	
———		*Melanosarcomas*	
———		*Lymphosarcomas*	
———		*Myelomas and chloromas*	
Lipomas		*Liposarcomas*	
Chondromas		*Chondrosarcomas*	
Osteomas		*Osteosarcomas*	
Leiomyomas		*Leiomyosarcomas*	
Rhabdomyomas		*Rhabdomyosarcomas*	
Hemangiomas		*Hemangiosarcomas*	
Lymphangiomas		*Lymphangiosarcomas*	
———		*(Endotheliomas)*	
———		*(Peritheliomas)*	
ENDOMETRIOSIS		MALIGNANT ENDOMETRIOSIS	

DIAGNOSIS

The diagnosis of ovarian tumors is usually made on the basis of the above-mentioned CLINICAL MANIFESTATIONS in conjunction with the past history. The diagnosis of accompanying hormonal disturbances will be discussed with the individual tumor types most likely to produce them.

Irrespective of possible endocrine derangements, the diagnosis rests chiefly upon PALPATION of the tumor region. Whenever possible, it should be performed bimanually after evacuation of the bladder and rectum, the patient being placed in a position suitable for palpation of the particular region in which the tumor is felt. Sometimes palpation may have to be performed under light anesthesia or, in the event of considerable ascites, after evacuation of the free peritoneal fluid by tapping.

X-RAY examination is especially useful in calcified tumors, embryomas and dermoids in which concretions, teeth and bones may be visible. The definite diagnosis, however, is usually possible only after morphologic examination of the tumor tissue itself, obtained by EXPLORATORY COLPOTOMY OR LAPAROTOMY

Differential Diagnosis. — The most common source of error in the diagnosis of ovarian and para-ovarian tumors are INFLAMMATORY PROCESSES (e g , salpingitis, perinephritis, pelvic abscesses), HYDROSALPINX (past history, usually bilateral tender tumors); ectopic or normal PREGNANCIES, (gonadotrophins in urine) and UTERINE FIBROIDS (connection with uterus, menorrhagias, frequent association with submucous fibroids). Tumors of the intestinal tract, "fecal tumors," a distended bladder, ascites or general obesity are less likely to be confused with ovarian tumors. In general, it is helpful in the diagnosis of large ovarian tumors, to remember as likely possibilities : "The Six "F-s" (Fat, Fetus, Fluid, Feces, Flatus, Fibroids).

PROGNOSIS

The prognosis of the various ovarian tumor types depends largely upon their benign or malignant nature, and in the latter case, upon their tendency to infiltrate and metastasize. In any case, if no treatment is applied, the course of true ovarian neoplasms is progressive. Spontaneous regression (e.g., rupture and subsequent involution of cysts, torsion with self-amputation and absorption of neoplasms) is extremely rare. If complete surgical removal is possible, the prognosis of most ovarian tumors is favorable, while X-ray or radium treatment rarely lead to permanent cures.

THERAPY

In spite of many enthusiastic statements concerning other types of treatment, the best therapy for any type of ovarian tumor is still its complete SURGICAL removal, whenever technically feasible. The operation should be performed as soon as possible, since it is almost never certain that the growth is not malignant or at least in the process of malignant transformation. It should be remembered, furthermore, that by postponing the operation the likelihood of complications (adhesions, hemorrhage, torsion, etc.) is increased. Of course, if a woman is in labor when the ovarian tumor is diagnosed, its removal may be postponed as long as the neoplasm does not mechanically interfere with delivery. During the first three months of gestation, ovariectomy entails the danger of abortion and if the tumor is not malignant, it may be advisable to postpone intervention until after delivery. Generally speaking, ovarian tumors should be removed by the abdominal and not by the vaginal route.

X-RAY and RADIUM therapy should be reserved for cases in which radical removal is technically impossible, because of widespread infiltrations and adhesions, metastases or great debility of the patient.

PARA-OVARIAN TUMORS IN GENERAL

In this book, the designation "para-ovarian tumors" is used to include all neoplasms situated in the immediate vicinity of the ovary, within its ligaments.

Many of these growths are described in the literature under such terms as tumors of the broad ligament, Wolffian body, parovarium (epoöphoron), paroöphoron, rete ovarii, pronephric remnants, Müllerian or Wolffian duct remnants, Gartner's duct remnants, etc. The most common designations are "parovarian tumors" and "broad ligament tumors." While many, if not all, the embryologic vestiges mentioned above may be the site of tumor formation, it is very questionable whether in the majority of the tumors described in the literature, the exact derivation from any one of these cell types could be proven with certainty.

The non-committal, rather all-inclusive term of para-ovarian tumors (which only implies that the neoplasm or cyst is in the immediate vicinity of the ovary), is therefore recommended for all those relevant blastomas in which the histogenetic mechanism is in doubt. It is particularly objectionable to use the term "parovarian" as synonymous with "para-ovarian" neoplasm, since the parovarium is a well defined morphologic structure derived from the Wolffian body and no neoplasm should be described as parovarian unless it demonstrably originates in this organ.

Although the histogenesis of para-ovarian tumors is often difficult to prove, the following types are theoretically possible:

A. PRIMARY PARA-OVARIAN TUMORS:

(1) Hydatid of Morgagni (pronephric ?).
(2) Kobelt's tubules (pronephric ?).
(3) The Wolffian body, also known as parovarium epoophoron or organ of Rosenmuller (mesonephric)
(4) The Wolffian duct (cranial part of mesonephric duct).
(5) Gartner's duct (caudal, usually obliterated, part of mesonephric duct).
(6) The junctional or rete tubules (usually obliterated connecting tubules between ovary and parovarium)
(7) The paroophoron (mesonephric)
(8) Accessory Fallopian tubes (Müllerian).
(9) Diverticula of the Fallopian tubes (Mullerian).
(10) Independent tumors of the connective tissue elements in the broad ligaments (e g., fibromas, lipomas, sarcomas, lymphangiomas).
(11) Tumors of accessory adrenal-cortical tissue

B SECONDARY PARA-OVARIAN TUMORS

(1) Metastases from distant malignant neoplasms
(2) Transplants of self-amputated benign neoplasms (usually of ovarian origin)
(3) Endometriosis (uterine mucosa transplants)
(4) Endosalpingiosis (tubal mucosa transplants).

For a discussion of the embryologic structures mentioned above, the reader is referred to the brief summary in this book (see: "Embryology") and to textbooks of Embryology.

The para-ovarian tumors are not sufficiently common nor of such endocrinologic interest as to justify a more lengthy description here.

HYPERFOLLICULOIDISM ASSOCIATED WITH OVARIAN GROWTHS (FOLLICLE CYSTS, SMALL-CYSTIC DEGENERATION OF THE OVARIES, FOLLICULOMAS)

DEFINITION

Hyperfolliculoidism in its purest form, is produced by various ovarian growths; only some of these are true neoplasms, but all of them will be discussed conjointly in this chapter because they represent closely allied conditions from the endocrinologist's viewpoint, although morphologically they are unrelated.

The principal relevant conditions are the following:

(1) FOLLICLE CYSTS (simple cysts of the follicles, retention cysts, persistent follicles, hydrops of the follicles) are enlarged and usually abnormally persistent Graafian follicles. There are transitional types between multiple follicle cysts and so-called "small-cystic degeneration of the ovaries."

(2) SMALL-CYSTIC DEGENERATION OF THE OVARIES (sclerocystic ovaries, polycystic ovaries, fibrocystic ovaries, oöphoritis follicularis, follicular hypertrophy of Ziegler, "ovaire à petits kysts de Trélat") is a *condition in which the connective tissue stroma of the ovary and its capsule is increased and many small follicle cysts develop through-* [illegible] ovarian cortex and are usually unaccompanied by any marked degree of fibrosis. Corpus luteum formation is deficient in both these conditions and both types may lead to the same clinical picture of hyperfolliculoidism.

(3) OVARIAN FOLLICULOMAS (granulosa cell tumors, basal cell tumors of the ovary, Kahlden's tumors, thecoma, fibroma thecocellulare xanthomatodes ovarii, Loffler-Priesel tumor) are true tumors of *the ovarian follicle, which may* produce excessive amounts of folliculoids. It has been customary to *distinguish sharply between gran*ulosa and theca cell tumors on the basis of purely morphologic characteristics. It is true that some folliculomas resemble the granulosa and others the theca of a normal follicle, but mostly there are granulosa and theca elements, as well as transition forms between the two in the same tumor.

PATHOLOGIC ANATOMY

OVARIAN FOLLICLE CYSTS rarely possess a diameter of more than 5 cm. They are lined by a *histologically characteristic* granulosa layer, which is surrounded by the theca interna. Occasionally, pressure atrophy may affect certain areas of the lining, but widespread atresia of the granulosa is rare.

SMALL-CYSTIC DEGENERATION leads to ovarian enlargement. The albuginea *is almost invariably greatly thickened* and scar-like; the whitish-grey surface is smooth and has a fascia-like appearance. *The cysts are scattered through*out the parenchyme and do not tend to protrude beyond the surface level. They represent persistent Graafian follicles. There is little evidence of any inflammatory change in the sclerotic stroma. Corpora lutea are usually absent.

OVARIAN FOLLICULOMAS vary from a few mm. to several inches in diameter. They can be solid or cystic and are *occasionally bilateral.*

Microscopically, the structure of folliculomas is extraordinarily variable. *They can consist predominantly of* granulosa or of theca-like cells, and sometimes imitate immature testicular *trabeculæ and tubules.*

The term "folliculome lipidique de Lecène" has been employed to describe *folliculomas in which the granulosa*-like cells contain many lipid granules. They resemble corpus luteum tumors *(luteomas) although their cells are* usually smaller.

Functionally, these tumors certainly belong *to the folliculomas, since they* produce cystic-glandular endometrial changes.

Although *many transitional types* are known, the following are the principal histologic forms of the folliculomas :

(1) Cystic: (*a*) microcystic, (*b*) macrocystic.

(2) Diffuse.

(3) Tubular.

(4) Trabecular (often "gyriform").

(5) Papillomatous.

(6) *Carcinomatous.*

(7) Theca cell type

(8) Sarcomatoid type

(9) *Mixed folliculomas* (in which no constituent is particularly predominant).

(10) *Various types of folliculomas* combined with other ovarian tumors (e g . teratomas, cystic adenomas).

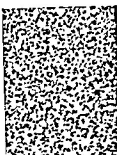
Polymorph granulosa-cell tumor. Within the same field we see tubular (center), diffuse (right) and microcystic (left and upper sides) cell arrangements
(After H Selye "Ovarian Tumors Encyclopedia of Endocrinology 1946)

"Gyriform" granulosa-cell tumor. High magnification of characteristic "pseudotubular" cell arrangement, columns consist of single cell layers arranged around a central axis without lumen (Courtesy of Dr P Masson)

Cystic granulosa-cell tumor. — A. Folliculoma with comparatively large cystic cavities. — B. Metropathia hemorrhagica (typical "Swiss Cheese" aspect) in patient whose folliculoma is illustrated in Fig A (Courtesy of Dr



Folliculoid granulosa cell tumor. — A. Characteristic folliculoid pattern ... epithelial field Some small cavities contain



"Folliculome lipidique" of Lecene. Partially-luteinized region in a granulosa-cell tumor Histologically this type is difficult to differentiate from luteomas, indeed, it may represent a transition to the luteoma.

(Courtesy of Dr H.-T. Karsner)

"Gyriform" granulosa-cell tumor. Note the characteristic gyriform arrangement of the granulosa cells. The epithelial columns are almost invariably two cells deep and thus resemble narrow tubules without central lumen

(Courtesy of Dr L.-C Simard)

Hyalinized thecoma with epithelioid cells. This roundish tumor (about 2 inches in diameter) exhibited the same pattern throughout Dense fibrous-tissue stroma with irregular islets of "epithelioid cells The 42-year-old patient suffered from polymenorrhea (bleeding every 18 days) and hypermenorrhea (duration of bleeding 8 days) Epithelioid cells were rich in fat granules.

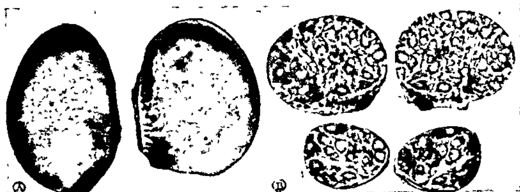
(Courtesy of Dr L Berger)



Thecoma. — A General view of a cross-section through ovary with small thecoma in the middle of the organ 66-year-old patient suffered from slight postmenopausal metrorrhagia (with passing of blood clots) — B Higher magnification of a small area in same tumor Note partly 'epithelioid' aspect of the cells (lower part of field) among spindle-shaped theca-cells — C Metropathia hemorrhagica 'Swiss cheese' endometrium small polypoid excrescences and some fairly large endometrial cysts in same patient (After H Selye Ovarian Tumors Encyclopedia of Endocrinology, 1946)

Partially luteinized granulosa cell tumor. Typical diffusely arranged granulosa cells (lower field) and partially luteinized cells (upper field) are seen side by side 54-year-old patient who never underwent a typical menopause but had irregular menses which lasted 15 to 21 days as a rule

(Courtesy of Dr L Berger)



(After E.-J. Kraus: Arch. f. Gynäk. *152*, 383, 1933.)



Small-cystic degeneration of the ovaries. Very low magnification of a histologic section through the ovary, showing cystic cavities of varying size, dense connective tissue stroma and thick capsule. The patient was 20 years old and suffered from a glioma of the brain.
(After E.-J. Kraus: Arch. f. Gynäk. *152*, 383, 1933.)



Gross appearance of benign polypoid hyperplasia of endometrium. Note physiologic line of demarcation at the internal os. The area in the square is shown under higher magnification in lower right corner.
(After E. Novak: Textbook of Gynecology. Williams & Wilkins, 1944.)

Malignant folliculomas may metastasize into lymph nodes, uterus, bones, etc.

INCIDENCE

Ovarian FOLLICLE CYSTS are very common, but since only few of them are removed for histologic study, the exact incidence is difficult to estimate. However, the vast majority of all cases of metropathia hemorrhagica (one of the most common disorders found in gynecologic practice) are undoubtedly due to follicular cysts.

Follicle cysts can occur in newborn infants, in whom they are probably caused by "synkainogenesis," the transit of maternal (in this case gonadotrophic) hormones to the embryo.

The occasional development of follicle cysts during pregnancy and under

the influence of chorionepitheliomas will be discussed elsewhere.

METROPATHIA HEMORRHAGICA and the causative follicle cysts have a double-peaked age-incidence curve, with a first, small maximum at or immediately after puberty, followed by a minimum between 31-35 years and a second, very high maximum at or after the menopause, between 45 and 65 years It is very probable that disturbances in the hormonal interrelations between the pituitary and the ovary are responsible for the high incidence of these cysts (and the resulting metropathia) at the onset and cessation of normal menstrual life

SMALL-CYSTIC DEGENERATION OF THE OVARIES also belongs to the more common gynecologic diseases, although here again the exact incidence is difficult to calculate. Supposedly relevant cases have been described in children, but the condition usually occurs only in adults.

OVARIAN FOLLICULOMAS are comparatively rare, but not as exceptional as had been thought. It is now estimated that about 10% of all primary ovarian carcinomas belong to the malignant granulosa-cell-tumor type. Benign granulosa cell tumors and thecomas are less common.

Folliculomas may occur at any age, but the vast majority develop prior to or during the menopause and about 1/3 of the cases are seen after the menopause.



Small-cystic degeneration of ovaries. Appearance of typical, small-cystic ovaries as seen at operation Note great enlargement of the glands, shiny tendon-like surface The cysts are all within the parenchyme and do not bulge out through the capsule
(Courtesy of Drs R.-W Schneider and E.-P McCullagh)

PATHOGENESIS

OVARIAN FOLLICLE CYSTS merely represent persistent, but otherwise normal, Graafian follicles. They are probably due to a derangement of the normal sequence in the elaboration of FSH and LH. This view is supported by the fact that metropathia hemorrhagica occurs most frequently at the beginning and end of normal menstrual life as well as in women who have had many children Presumably, under these conditions FSH formation tends to be excessive and continuous while LH is produced in subnormal amounts.

METROPATHIA HEMORRHAGICA is due to the persistent action of folliculoids upon the endometrium. It is independent of the nature of the underlying ovarian lesion as long as the latter occasions an excessive or prolonged production of folliculoids. The manifestations of metropathia hemorrhagica produced by endogenous folliculoids, are identical with those seen in castrate women following continuous, excessive folliculoid hormone treatment. In this connection, it is of interest that partial

ovariectomy frequently causes persistent follicle-cyst formation in the remaining ovarian tissue; this also leads to metropathia hemorrhagica, due to hyperfolliculoidism. (See : p. 376)

SMALL-CYSTIC DEGENERATION OF THE OVARIES has been ascribed to various types of inflammatory lesions conducive to an excessive development of connective tissue, especially in the ovarian capsule. It is thought that this capsular fibrosis may mechanically interfere with follicle rupture and thus cause the *persistence of follicles.*

OVARIAN FOLLICULOMAS could perhaps arise from "Walthard's cell nests" (granulosa-like formations originating in the germinal epithelium), or from *mature granulosa and theca cells.*

As regards the functional pathogenesis of folliculomas, the high incidence at, or just prior to the menopause, and the occasional occurrence of theca-adenomas during pregnancy, imply that pronounced changes in the hormonal equilibrium (increased gonadotrophin *production ?*), such as occur at these times, play an etiologic rôle.

It is of interest that folliculomas have been produced by X-ray treatment in a certain strain of mice. These tumors appear to develop from surviving granulosa cells and are true, transplantable neoplasms. They produce folliculoids as judged by the resulting estrous changes and cystic hyperplasia of the endometrium. (See. p. 384.)

Racial factors presumably are also of importance in the development of folliculomas. In women, these growths tend to occur in several members of the same family and certain strains of mice have been observed to possess a special tendency to develop spontaneous, transplantable, malignant papillomatous granulosa cell tumors which produce signs of hyperfolliculoidism.

CLINICAL COURSE

The most prominent clinical manifestation of all types of ovarian growths accompanied by hyperfolliculoidism (follicle cysts, small-cystic degeneration, folliculomas), is the development of METROPATHIA HEMORRHAGICA (synonyms : cystic-glandular hyperplasia or "Swiss cheese" endometrium, endometrial hyperplasia, functional uterine bleeding, polypoid hyperplasia of the endometrium, etc.). This is a condition in which the *endometrial changes characteristic of the follicular phase* of the menstrual cycle are excessively developed. Usually, the total height of the endometrium is far above normal, many glands are cystically dilated ("Swiss cheese" appearance), mitotic figures in the epithelial cells are plentiful and there is a great tendency to irregular, more or less continuous, uterine bleeding. Not infrequently, the uterus also shows other changes presumably due to hyperfolliculoidism, such as endometrial polyps, epithelial metaplasia, fibroids or endometriosis. *(See also : Endometriosis on p. 467.)*

Among the clinical manifestations of metropathia hemorrhagica, persistent *uterine bleeding* (rarely accompanied by pain), *sterility* and a follicular-phase type of *vaginal smear* are especially characteristic.

Postmenopausal bleeding is very common in older women with hyperfolliculoidism. It frequently gives rise to confusion with uterine carcinomas.

Progestational changes are absent in typical instances of metropathia hemorrhagica, since corpus luteum formation is suspended

Metropathia hemorrhagica may eventually lead to *uterine cancer.* Although this is uncommon, endometrial carcinomas appear to be somewhat more frequent with various types of hyperfolliculoidism than in otherwise

the influence of chorionepitheliomas will be discussed elsewhere.

METROPATHIA HEMORRHAGICA and the causative follicle cysts have a double-peaked age-incidence curve, with a first, small maximum at or immediately after puberty, followed by a minimum between 31-35 years and a second, very high maximum at or after the menopause, between 45 and 65 years. It is very probable that disturbances in the hormonal interrelations between the pituitary and the ovary are responsible for the high incidence of these cysts (and the resulting metropathia) at the onset and cessation of normal menstrual life.

SMALL-CYSTIC DEGENERATION OF THE OVARIES also belongs to the more common gynecologic diseases, although here again the exact incidence is difficult to calculate. Supposedly relevant cases have been described in children, but the condition usually occurs only in adults.

OVARIAN FOLLICULOMAS are comparatively rare, but not as exceptional as had been thought. It is now estimated that about 10% of all primary ovarian carcinomas belong to the malignant granulosa-cell-tumor type. Benign granulosa cell tumors and thecomas are less common.

Folliculomas may occur at any age, but the vast majority develop prior to or during the menopause and about 1/3 of the cases are seen after the menopause.

PATHOGENESIS

OVARIAN FOLLICLE CYSTS merely represent persistent, but otherwise normal, Graafian follicles. They are probably due to a derangement of the normal sequence in the elaboration of FSH and LH. This view is supported by the fact that metropathia hemorrhagica occurs most frequently at the beginning and end of normal menstrual life as well as in women who have had many children. Presumably, under these conditions FSH formation tends to be excessive and continuous while LH is produced in subnormal amounts.



Small-cystic degeneration of ovaries. Appearance of typical, small-cystic ovaries as seen at operation. Note great enlargement of the glands, shiny tendon-like surface. The cysts are all within the parenchyme and do not bulge out through the capsule.
(Courtesy of Drs R.-W. Schneider and E.-P. McCullagh)

METROPATHIA HEMORRHAGICA is due to the persistent action of folliculoids upon the endometrium. It is independent of the nature of the underlying ovarian lesion as long as the latter occasions an excessive or prolonged production of folliculoids. The manifestations of metropathia hemorrhagica produced by endogenous folliculoids, are identical with those seen in castrate women following continuous, excessive folliculoid hormone treatment. In this connection, it is of interest that partial





Precocious pseudopuberty due to granulosa cell tumor. — A, 4-year-old girl exhibiting precocious genital development. Menstruation began *at age of 3 years.* Granulosa cell cyst of ovary found. — B, Bone age 8½ years (although actual age 4 years). Accelerated somatic development due to granulosa cell cyst.
(Courtesy of Dr R.-C. Grauer.)

normal women. This is of interest in view of the carcinogenic effect of folliculoids.

Oligomenorrhea or *amenorrhea* are rare in women with persistent follicle cysts, small-cystic degeneration or ovarian folliculomas.

In children, follicle cysts or folliculomas often cause precocious PSEUDOPUBERTY, with the occurrence of uterine bleeding (not menstruation, since there is no progestational phase), premature development of the breasts, pubic hair, clitoris, labia, adult female body contours, and sexual drive.

NERVOUS MANIFESTATIONS are especially common in women suffering from hyperfolliculoidism (irrespective of the underlying ovarian lesion). Among these, excessive libido (nymphomania) is particularly prominent. Hysteria, gastrointestinal spasms, ovaralgia (pain in the ovarian region), and what the French investigators designate as "toux uterine" or "uterine cough" may perhaps also be related to certain types of hyperfolliculoidism, but a causal connection with the hormonal derangement is less clearly demonstrable as





Metropathia hemorrhagica. — A Specimen obtained by curettage for profuse uterine bleeding Note widely dilated cystic glandular spaces some filled with blood — B Recurrence of metropathia in same patient following discontinuation of successful progesterone therapy (Courtesy of Drs G -S. Henry and J -S -L. Browne.)





Sterility treated with progesterone and LH. — A 9th day of luteal phase after 7 daily injections of 10 mg of progesterone Note cystic glandular endometrium, which here did not respond well to progesterone — B Same patient on 12th day of luteal phase after 12 daily injections of 1000 I U of LH Note marked progestational (decidual) proliferation apparently mediated by the patient's own ovary (Courtesy of Drs G S Henry and J -S -L Browne)

adrenal-cortical tumors tend to produce virilism accompanied by increased 17-KS *excretion.*

In postmenopausal women, continuous bleeding must always raise the question of a possible UTERINE CARCINOMA, POLYPS, submucous FIBROMA, SENILE ENDOMETRITIS, etc. The diagnosis of these conditions is facilitated by endometrial biopsies, hystero-salpingography and the general clinical history.

It is also noteworthy that hyperfolliculoidism caused by any type of ovarian growth leads to the same clinical symptomatology, and hence the differential diagnosis between ovarian folliculomas, persistent follicle cysts, and small-cystic degeneration may not be possible without an exploratory laparotomy. Very atypical granulosa cell carcinomas often cause no endocrine disturbance because their cells are too undifferentiated to elaborate hormones.

Differentiation of the ovarian growths which produce hyperfolliculoidism from ectopic or normal PREGNANCY (increased gonadotrophin excretion), and APPENDICITIS is rarely difficult.

Metropathia hemorrhagica is frequently confused with CARCINOMA OF THE UTERUS, UTERINE POLYPS, INCOMPLETE ABORTION, SUBMUCOUS MYOMAS, etc., but here again endometrial biopsies and hormone analyses of blood and urine usually permit a definite diagnosis.

SYSTEMIC DISEASES CONDUCIVE TO BLEEDING (e g , blood dyscrasias, hemophilia) should also be considered.

PROGNOSIS

The OVARIAN FOLLICLE CYSTS, especially those occurring at puberty, often regress spontaneously. In the adult, the prognosis is also favorable, although occasionally, intractable bleeding may result in fatal anemia unless suitable therapy is instituted. Even in adults, spontaneous cures do occur. *Approximately the same may be said* about the prognosis of metropathia hemorrhagica as such, whether due to follicle cysts or small-cystic degeneration of the ovaries

OVARIAN FOLLICULOMAS *show no* tendency to regress spontaneously. The rate of their growth and development is very variable. The highly *differentiated* granulosa and *theca cell* tumors grow slowly and have little tendency to metastasize, while *malignant* granulosa carcinomas and *theca sarcomas* grow rapidly, metatasize *and infiltrate* neighboring organs. *Following* the extirpation of malignant *folliculomas,* survivals of 10 to 20 years have repeatedly been reported.

THERAPY

Follicle cysts. — *In children,* after removal of individual *persistent* follicle cysts, the accessory *sex* organs return to the infantile state; in adults, the normal menstrual *rhythm reappears* in the majority of the cases. Puncturing of the follicles and partial ovariectomy have occasionally been reported as bringing temporary relief, but are less satisfactory. Complete OVARIECTOMY is unjustified, except in menopausal cases. X-RAY treatment may be beneficial, but is indicated chiefly in postmenopausal cases, since in young women the danger of subsequent sterility is too great.

With comparatively small persistent follicles, the cyclic administration of LUTEOID HORMONES should be attempted, sometimes it may even lead to a permanent cure.

Metropathia hemorrhagica. — The metropathic endometrium should first be removed by CURETTAGE. Usually, this in itself brings only temporary relief, but it is necessary for diagnostic

regards these manifestations. Pigmentation of the skin, "chloasma uterinum," is not very frequent in hyperfolliculoidism.

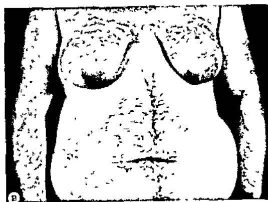
Other clinical manifestations are *chiefly due to the mere mechanical presence of the ovarian neoplasm* (see : Ovarian Tumors in General on p. 417).

DIAGNOSIS

In addition to the LOCAL SIGNS characteristic of an ovarian tumor (see : Ovarian Tumors, p. 419), the growths conducive to hyperfolliculoidism manifest themselves by the specific signs of hormone overdosage (precocious pseudopuberty, metropathia hemorrhagica, postmenopausal bleeding, increased folliculoid and decreased gonadotrophin elimination in the urine).

From the differential diagnostic point of view, the ADRENOGENITAL SYNDROME deserves attention. It will be remembered, that unlike folliculomas,









Extreme hirsutism with sclerocystic ovaries. — A, B, C and D. 28-year-old woman, height 64", weight 211 lbs, who suffered from obesity, amenorrhea, endometrial polyps, multiple bilateral follicle cysts, and extreme *hirsutism*. There was no evidence of adrenal tumor at surgical exploration

(Courtesy of Dr E.-P McCullagh.)

luteoid treatment has also been recommended. 5.0 mg. of stilbestrol daily for 10 days supplemented with 5 0 mg. of progesterone during the last 5 days is usually followed by uterine bleeding within 3-4 days after discontinuation of treatment. This procedure may be repeated once monthly to imitate a cycle, but often spontaneous menses are at least temporarily re-established.

Short treatment with very high doses of *folliculoids* — the so-called "follicULIN shock treatment" — may also be attempted but has not yet been tried on a large scale.

A truly rational therapy will only be possible when the various *gonadotrophins* become available in a pure form In the past, these have not given very encouraging results. More recently, it has been claimed that *luteotrophin* is beneficial in "functional bleeding."

Ovarian Small-Cystic Degeneration. — In most cases of small-cystic degeneration of the ovaries, the condition is resistant to all efforts of internal therapy.

Complete BILATERAL OVARIECTOMY was the treatment of choice towards the end of the last century, but except in postmenopausal women, such a radical intervention is hardly ever advisable.

IGNIPUNCTURE of the follicles or LIGATURE OF THE OVARIAN ARTERY may give at least temporary relief in some cases, but the method of choice is PARTIAL RESECTION or DECORTICATION of the ovary. For this a variety of technics have been devised, among which bilateral wedge-excision, with subsequent union of the ovarian wound by suture, is generally considered to be the best. Another modification of this procedure consists in turning the ovary inside out after the wedge-excision, and stabilizing it in this position so as to bury the sclerotic serosal surface and expose the presumably normal follicles of the medulla.

The ovaralgia which frequently accompanies small-cystic degeneration can often be completely cured by bilateral DENERVATION OF THE OVARIES and this intervention may also have a beneficial effect upon the ovarian lesion itself.

Among other therapeutic methods, X-RAY or RADIUM treatment of the ovaries have been claimed to be effective. In view of the danger of destroying too much ovarian tissue however, it appears inadvisable to resort to such drastic means as a routine procedure. Considering our deep ignorance of the underlying endocrine disturbance, it is not surprising that HORMONAL THERAPY has so far proved rather ineffective.

Ovarian Folliculomas. — Here, whenever possible, the therapy of choice is the complete surgical removal of the ovary which bears the neoplasm Radiation therapy should not be employed except in patients with widespread, inoperable, malignant folliculomas or in those in whom metastases and recurrences following operation make additional surgical interventions impossible.

HYPERLUTEOIDISM AND CORPUS LUTEUM CYSTS

DEFINITION

Corpus luteum cysts are transformation products of corpora lutea resulting from the excessive accumulation of fluid in the central cavity Their life span is usually longer than that of the normal corpus luteum of menstruation, but the luteal tissue which lines their wall is not capable of the unlimited growth characteristic of true blastomas. They are usually simple cysts and should be distinguished from the multiple cystic corpora lutea found in the ovaries of women who suffer from hydatidiform moles or chorionepitheliomas.

purposes and increases the efficacy of subsequent endocrine therapy. It also diminishes the likelihood of the otherwise often alarming, profuse withdrawal-bleeding which tends to occur in these patients after a course of ovarian hormone injections. Sometimes however, even mere curettage effects a permanent cure.

HYSTERECTOMY or "DEFUNDATION OF THE UTERUS" should not be performed to check metropathia hemorrhagica except where there are intractable postmenopausal hemorrhages, or when the possibility of cancer can not be ruled out.

PARTIAL RESECTION OF THE OVARY has been practiced in order to remove the source of excess folliculoids. In the light of contemporary knowledge, this intervention is not advisable, since we know that even in normal individuals, the ovarian remnant tends to become cystic after partial ovariectomy.

X-RAY treatment of the pituitary has been suggested as a means of inhibiting hypophyseal hormone production and its effect upon the ovary. Since the optimal dosage is difficult to determine, this therapy is fraught with the danger of eliciting permanent damage. X-ray castration on the other hand is not dangerous, and yields almost 100% cures, hence this technic is highly advisable if the patient is past the menopause or if for other reasons, her future sterility is not a deterring factor.

The RADIUM TREATMENT of metropathia hemorrhagica is less popular, although it has been claimed that with intra-uterine application of 200-400 mg. hours there is a satisfactory reduction of the bleeding without premature menopause in 80% of the adult patients.

The method of choice is ENDOCRINE THERAPY. In young girls, whenever possible, this should be given without preliminary curettage, since such operations often cause severe mental upset at this age. In adult women, on the other hand, it is advisable to remove the pathologic endometrium. This precaution is particularly indicated whenever polypoid excrescences assume large dimensions. If curettage is to be avoided, it may be well to give *testoids* for a short period with the view of obtaining involution of the endometrium instead of its mechanical removal. It should be kept in mind, however, that some prominent gynecologists are strongly opposed to the use of testoids in females for any reason. In any case, such therapy must be limited to the absolutely necessary minimum (about 5 mg./day), in order to avoid virilization

The most advisable procedure is to administer *progesterone* in repeated courses, each consisting of four doses of 5-10 mg. given every other day, in order to substitute for the lack of endogenous corpus luteum hormone production. These progesterone treatment periods must be separated by about 18 days of rest, during which the endogenous folliculoids have time to develop a proliferative endometrium. It is true that even this therapy is merely symptomatic, since it deals only with the result of the ovarian derangement. However, for reasons which are not yet quite clear, in many instances intermittent progesterone therapy re-establishes the normal interrelations between the ovary and pituitary and thus results in a more or less permanent cure

"Metropathia non-hemorrhagica" that is, cystic-glandular hyperplasia of the endometrium with amenorrhea, is less common and probably due to chronic folliculoid hormone action of a very even degree. Unlike in amenorrhea due to hypofolliculoidism, bleeding may be obtained by treatment with progesterone alone Alternate folliculoid and



Carcinoma of the corpus luteum? Very low magnification of the tumor wall Note greatly corrugated surface which resembles the wall of a corpus luteum cyst In left lower corner several independent cystlets developed, their walls are similar to that of the main cavity but somewhat thinner

(Courtesy of Dr P Masson)

from unselected autopsy material, found corpus luteum cysts in 9% of them However, it is sometimes difficult to differentiate with certainty between normal and persistent cystic corpora lutea, there being many transitional stages

PATHOGENESIS

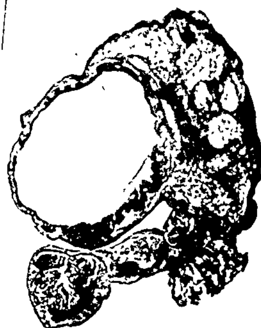
The etiology of corpus luteum cysts is still insufficiently understood. It is known that in women suffering from gonadotrophin-producing tumors, the ovaries almost invariably contain a large number of cystic corpora lutea (see: Ovarian changes in chorionepitheliomas, hydatidiform moles and pituitary tumors). Furthermore, treatment with gonadotrophins produces "mulberry ovaries" in various laboratory animals. Unusually large, cystic corpora lutea can be produced in the rat by simultaneous treatment with gonadotrophins and folliculoids Similar hormonal factors are likely to be the cause of multiple corpus luteum cysts in patients suffering from tumors of placental origin. This view is consonant with the comparative frequency of persistent corpora lutea and corpus luteum cysts in normal and in ectopic pregnancy as well as immediately following incomplete abortion (see: Ovarian changes in pregnancy). In all these instances, the simultaneous production of gonadotrophins and folliculoids may well be the cause of the ovarian change. It remains to be shown, however, whether the typical, usually single, corpus luteum cyst is due to a similar pathogenic mechanism, and if so, what determines the number of corpora lutea which undergo cystic change.

Some authors claim that pseudopregnancy, elicited by sexual intercourse or nursing, may also be the cause of persistent corpora lutea in women as it undoubtedly is in animals.

CLINICAL COURSE

Women with corpus luteum cysts frequently believe themselves to be pregnant. The outstanding clinical manifestations of persistent corpora lutea are those of pseudopregnancy. There is amenorrhea, with PROGESTATIONAL TRANSFORMATION of the endometrium, which fails to break down at monthly intervals. Occasionally, severe metrorrhagias occur after a period of amenorrhea, presumably due to a variation in the ovarian hormone production or the eventual complete breakdown of the corpus luteum cyst.

It has been claimed that in 3.2% of the cases, persistent corpora lutea are associated with internal or external ENDOMETRIOSIS and that sometimes they





Corpus luteum cyst. — A. Low magnification of an ovary containing a medium-sized corpus luteum cyst The cyst wall is lined by an irregular, but in general fairly high, corpus luteum cell border The latter is thinnest on the left side and thickest in the lower right section of the cyst The mesosalpinx and a cross-section through the oviduct are seen below the cyst. — B. Higher magnification of the wall of the corpus luteum cyst shown in Fig A. Note the typical corrugated appearance of the corpus luteum lining which forms a stratified, fairly thick epithelial layer. The cell borders and nuclei are of normal appearance.

(Courtesy of Dr L.-C Simard)

Corpus luteum cysts are the most common cause of hyperluteoidism, since most of the true blastomas of the cor-pus luteum (luteomas) are not hormone-producing. It is, therefore, in connec-tion with these cystic and persistent cor-pora lutea that we shall discuss the syndrome of hyperluteoidism

PATHOLOGIC ANATOMY

The histologic structure of corpus uteum cysts is comparatively simple. It esembles that of a large corpus luteum whose cavity is greatly distended by uid. The wall consists of more or less ypical, lipid-containing (macroscop-ally yellow) corpus luteum cell tis-e, which may be either in direct con-ct with the central fluid accumulation, or separated from it by a simple epithe-lial lining or a band of connective tis-sue. It has been claimed that the per-sistent corpus luteum resembles that of gestation inasmuch as it is comparative-ly poor in lipid granules and rarely con-tains a central hemorrhage Lipid-con-taining "pseudoxanthoma" cells in the walls of endometriomas, abscesses or infected ovarian cysts are often mis-taken for corpus luteum cysts.

INCIDENCE

Persistent corpus luteum cysts are not very commonly observed, although persistently progestational endometria can hardly be ascribed to any other ovarian lesion. One worker, who ex-amined 100 pairs of ovaries gathered

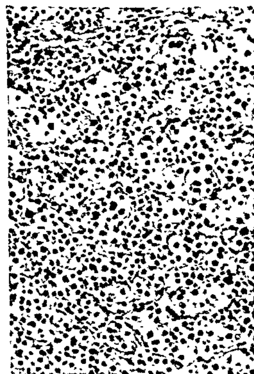
"HYPERNEPHROMAS," "LUTEOMAS" AND OTHER "LIPID CELL TUMORS" OF THE OVARY

DEFINITION

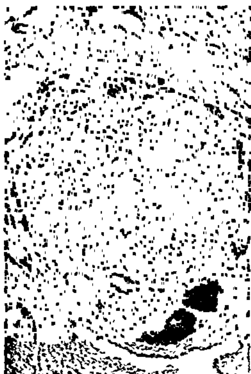
The "lipid cell tumors" constitute a group of ovarian neoplasms characterized mainly by their lipid-granule-containing endocrine cells which resemble those of the corpus luteum, the adrenal cortex, the *theca folliculi* or the Leydig cells. Most of them are virilizing growths. With the methods now available it is impossible to determine the origin of these tumors with certainty. Therefore, without excluding the possibility that they are morphogenetically heterogeneous, they will be discussed conjointly under the non-committal heading of lipid cell tumors. The common corpus luteum cysts, and the adenomatous proliferation of theca lipid cells or ovarian Leydig cells are discussed in special chapters, merely because *their identity is more clearly* established. The term "hypernephromas" of the ovaries is to be avoided, since this designation has been reserved for the so-called Grawitz tumors of the kidney (see : p. 191).

PATHOLOGIC ANATOMY

MACROSCOPICALLY, the lipid cell tumors of the ovary are usually more or less irregularly shaped, solid growths which can be readily differentiated from the corpus luteum cysts (see above). They rarely reach a size of



Hypernephroma of the ovary. Adrenal-cortical cells similar to those seen in accessory adrenals At this high magnification the cell details are evident The tumor appears to be benign and would be difficult to differentiate from an ordinary accessory adrenal (Courtesy of Dr H.-T Karsner)



ticular woman of 45 years, no obvious clinical manifestations resulted from this comparatively small cell proliferation (Courtesy of Dr L. Berger)

may even cause METROPATHIA-HEMORRHAGICA-LIKE CHANGES in the endometrium. One author goes so far as to claim that 14% of his patients with "functional uterine bleeding" exhibit a secretory, not a proliferative, endometrium Among these, corpus luteum cysts were commonly demonstrable. The pathogenesis of these changes is not fully understood, although certain animal experiments indicate that progesterone may produce a "Swiss cheese" endometrium if the uterus is subjected to trauma while it is under the influence of the hormone.

As in pregnancy, the BREASTS are enlarged and may secrete colostrum.

COMPLICATIONS

Since the walls of corpus luteum cysts are thin and fragile, they tend to RUPTURE easily. Even careful pelvic examination may suffice to rupture corpus luteum cysts and to elicit an intraperitoneal hemorrhage. There is reason to suspect, however, that in many allegedly pertinent cases the patient actually suffered from an ectopic gestation.

DIAGNOSIS

It is rarely possible to diagnose a corpus luteum cyst, without exploratory laparotomy.

Upon PELVIC EXAMINATION, a corpus luteum cyst reveals itself as an approximately walnut-sized, smooth, somewhat mobile, adnexal tumor which may be painful. The uterus is often enlarged. It should be kept in mind that these cysts rarely reach a diameter of more than about 2½ inches and many of the large tumors described as corpus luteum cysts are in reality abscesses with a lipid-containing lining.

Most relevant cases are operated upon under the diagnosis of ECTOPIC GESTATION because almost all the symptoms and signs of these two conditions are identical. Even the gonadotrophin excretion in the urine may be augmented in the presence of corpus luteum cysts as it is in pregnancy. This fact gives further support to the view that hypophysoid hormones play an important rôle in the pathogenesis of these cysts. Since, on the other hand, ectopic pregnancy often fails to elicit a marked increase in urinary gonadotrophins, even a negative Aschheim-Zondek test is of little diagnostic value. Systematic pregnanediol determinations in the urine of women with corpus luteum cysts have not yet been made but they would probably give helpful information.

PROGNOSIS

In many cases corpus luteum cysts persist for a very long time and tend to recur, as judged by the menstrual histories. Permanent, spontaneous cures may occur. The otherwise favorable prognosis is somewhat darkened by the ever-existing possibility of a severe, potentially fatal, peritoneal hemorrhage.

THERAPY

The usual therapy of corpus luteum cysts is SURGICAL excision of the cyst itself, leaving the remaining ovarian tissue intact. This leads to a "withdrawal hemorrhage" after which the menstrual cycles may become normal owing to the re-establishment of a physiologic relationship between the ovaries and the pituitary. If the primary cause of the condition is entirely extra-ovarian, however, it tends to recur following removal of the cyst.

Could the condition be recognized with certainty, the advisability of a surgical intervention would be very doubtful, especially since complications, such as serious ovarian or uterine hemorrhages, are rare. Most cases, however, are recognized only on the operating table and then, removal of the cystic corpus luteum is certainly justified.



— H. The high lipid content of the tumor cells is shown in this section stained with sudan III — I. Glycogen is indicated by the small, dark tumor cells, stained with carmine — J. Darkened cells indicate a positive reaction in section

marrow elements; stained with hematoxylin and eosin.

more than about 6 inches in diameter and the smallest examples are minute nodules, hardly distinguishable from the non-blastomatous adrenal rests. Perhaps their most characteristic macroscopic feature is their bright yellow color which strikingly resembles that of the corpus luteum or adrenal cortex.

Often, lipid cell tumors develop bilaterally. They are most frequent within the mesovarium or the broad ligament, where accessory adrenocortical tissue and nests of ovarian Leydig cells are common.

Microscopically, they usually consist of more or less irregular bands or islets of vacuolated, large, polyhedral cells which imitate the structure of the corpus luteum or adrenal cortex. In vivo, the vacuoles are filled with lipid granules and sometimes considerable quantities of glycogen. The latter is allegedly characteristic of tumors derived from the adrenal cortex, permitting their differentiation from growths of the corpus luteum. Fuchsinophilic granules, supposedly characteristic of the adrenals in the adrenogenital syndrome, are present only in some of the ovarian lipid-cell-tumors.

These tumors are often polymorph and certain portions can exhibit the aspect of an alveolar sarcoma, a medullary, papillary or a cirrhous carcinoma. Without any very definite reason, some lipid cell tumors have been described as CORPUS LUTEUM TUMORS or "luteomas", others as CARCINOMAS OF THE CORPUS LUTEUM and still others as OVARIAN HYPERNEPHROMAS OR SARCOMAS.

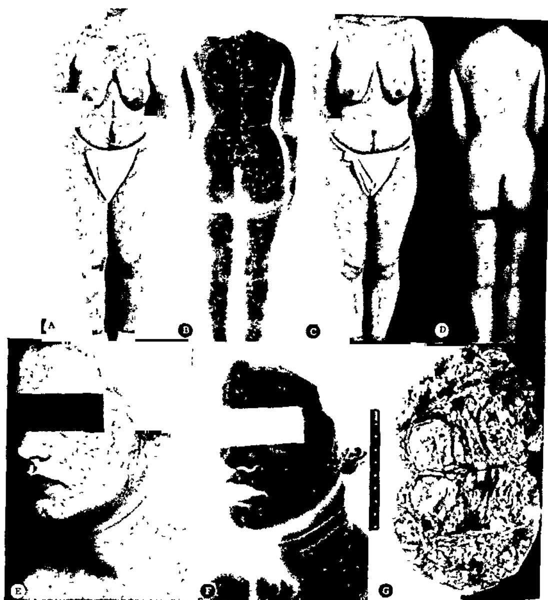
As emphasized in the chapter on folliculomas, certain granulosa cell tumors may become partially luteinized and assume the aspect of the "FOLLICULOME LIPIDIQUE" of *Lecène*. It is obvious that if this process of luteinization goes far enough, transitional types will result which are difficult to classify. Luteinized granulosa-cell-tumors and corpus luteum tumors are, however, so closely related that it would be difficult to make even a theoretic distinction between them.

INCIDENCE

Lipid cell tumors are very rare and can appear at any age. Most frequently they occur in adult women, often after the menopause.

PATHOGENESIS

It is debatable whether solid lipid cell tumors can develop from fully-formed corpora lutea, in spite of the many reports on so-called "luteomas." It must be clearly stated that in most cases no reason is given by authors for their designation of a growth as "luteoma" rather than adrenal-rest tumor



Ovarian lipid-cell tumor. — A. and B. Appearance of patient's body before operation The patient suffered from hypertension (160/110), hirsutism, acne, clitoris enlargement, secondary amenorrhea, obesity, and a palpable ovarian tumor She excreted 55 mg of 17-KS/day (about 5 times normal) Weight 141 pounds (64 Kg) — C. and D. Appearance of body five months after ablation of ovarian tumor By this time her virilism had vanished, her blood pressure was normal (139/90), the urinary 17-KS 2 6mg/day, her body weight 132 pounds (59.9 Kg) and her previously virile attitude became feminine. — E. Appearance of face before operation (hirsutism, acne) — F. Five months after operation — G. Cut surface of tumor removed from patient shown in previous figures The dark areas represent hemorrhages within the tumor substance, remaining portion was of bright orange-yellow color (Cont'd)

(After E.-J Kepler et al Am J Obst & Gynec 47 43, 1944)

in some women, this condition is accompanied by signs of virilism and especially hirsutism. At the same time, the ovaries reveal a tendency toward theca luteinization.

Under the name of "hyperthecosis," *Fraenkel (1941)* described a syndrome of virilization elicited by diffuse hyperplasia of the theca cells. He apparently considered the theca proliferation as truly blastomatous, since occasionally he referred to it as "thecomatosis." In order to distinguish these cases from thecomas (which cause hyperfolliculoidism) the term "TESTOID HYPERTHECOSIS" will be used here.

In most relevant cases, ovariectomy is followed by at least partial disappearance of the pseudohermaphroditic traits. Yet the ovarian origin of the clinical symptoms is sometimes subject to doubt. In one bearded woman with normal menses there was a typical Cushing's syndrome. The ovaries were greatly enlarged, due to small-cystic degeneration with theca luteinization. She died from pulmonary embolism shortly after removal of her ovaries and autopsy revealed a basophilic pituitary adenoma and adrenal-cortical hyperplasia. In another case, the clinical manifestations and the ovarian changes were very similar. Ovariectomy led only to *temporary regression* of the virilism (depression of testoid production during postoperative alarm reaction?). She suffered from severe headaches but since she survived, the presence of a primary pituitary lesion could not be checked.

Further work will have to be done before the pathogenesis of this interesting syndrome is understood, but it is suggestive that theca luteinization induced by gonadotrophins can cause virilism in animals. Thus we have experimental, as well as clinical, evidence indicating that the theca can produce *both folliculoid and testoid* hormones. In cases with primary hypophyseal hyperfunction the possibility of simultaneous ovarian and adrenal-cortical hyperactivity must also be kept in mind.

In connection with testoid hyperthecosis, it is pertinent to mention that hyperplasia and the formation of small ADENOMAS IN LEYDIG CELLS OF THE HILUS are also conducive to virilism. These cells are not known to give rise to large or malignant tumors and the resulting virilism is generally moderate. There is usually some growth of the clitoris, deepening of the voice, hirsutism and breast atrophy, but the menstrual cycle may continue normally. Frequently the cause of such changes remains unknown. Perhaps hilus-cell hyperplasia would prove to be more common if these cells were examined in all cases of inexplicable virilism.

The DIAGNOSIS of testoid hyperthecosis or Leydig cell hyperplasia is impossible with our present day methods except by biopsy. *From the differential* diagnostic viewpoint arrhenoblastomas, adrenal tumors, congenital true- and pseudohermaphroditism and virilizing folliculomas must be considered. (See patients on pp. 446, 447.)

The THERAPY is ovariectomy whenever the symptoms are sufficiently severe to justify it.

OVARIAN TUBULAR ADENOMAS (ARRHENOBLASTOMAS)

In this book, the term "tubular adenoma" is used to designate any ovarian tumor whose epithelial components consist prevailingly of gland-like tubules free of mucin.

An attempt has been made to define as "arrhenoblastomas" or "andreioblastomas" all those neoplasms which are "masculinity tumors" (Männlichkeitsgeschwulste), without distinguish-

and vice versa. Probably the majority, if not all, of these growths are derived from adrenal-cortical remnants (Marchand's rests). This view is supported by the previously mentioned fact that many lipid cell tumors occur in the broad ligament where Marchand's rests are particularly common.

CLINICAL COURSE

In addition to the usual local manifestations of an ovarian tumor, the lipid cell growths — if hormonally active — are mainly characterized by signs of VIRILIZATION, which frequently are so pronounced that one may well speak of pseudohermaphroditism. There can be marked hirsutism of the trunk and extremities, beard growth, enlargement of the clitoris, deepening of the voice, amenorrhea, and atrophy of the breasts.

In children, lipid cell tumors cause PRECOCIOUS PSEUDOPUBERTY with growth of the breasts (unlike in adults[1]), pubic hair and libido At this early age, however, pseudohermaphroditism has not been noted with these ovarian growths.

In many bearers of such lipid cell *tumors, there are also other symptoms* of the adrenogenital syndrome (or Cushing's syndrome) such as *HYPERTENSION, POLYCYTHEMIA, OBESITY, CUTANEOUS STRIAE* and DIABETES These manifestations are clearly reminiscent of adrenal hyperfunction and strongly suggest that the ovarian lipid cell tumors can imitate adrenal growths in producing gluco-corticoids and mineralo-corticoids as well as sex hormones

DIAGNOSIS

The diagnosis of lipid cell tumors is extremely difficult, as shown by the fact that only in one case was at least a probable diagnosis of "adrenal-cortical tumor of the ovary" made on the basis of clinical evidence. Such a diagnosis would appear warranted in patients in whom signs resembling the adrenogenital syndrome or Cushing's syndrome develop simultaneously with an ovarian tumor.

Cushing's disease and primary adrenal-cortical tumors have to be eliminated on the basis of the usual local symptoms pointing to a tumor in the adrenal or pituitary region. It is well to remember that hypophyseal growths can secondarily cause luteinization of the ovaries and subsequently lead to virilization of the testoid hyperthecosis type. (See patients on pp 446, 447)

HORMONAL studies can also be of some diagnostic value. There is some *indication that 17-KS excretion is increased*, but comparatively few relevant data are available as yet.

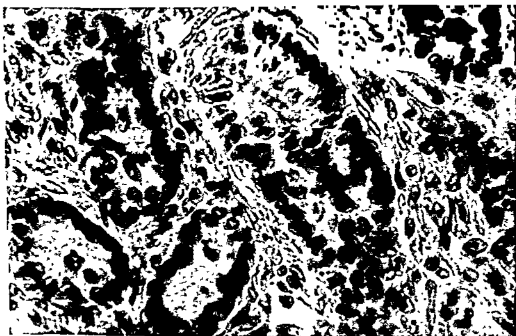
PROGNOSIS AND THERAPY

Lipid cell tumors do not regress spontaneously, but following surgical ablation the results are very encouraging. If the patient survives the complete removal of the growth, the symptoms almost invariably vanish.

There is, however, a comparatively high mortality rate postoperatively, perhaps because a sudden drop in the corticoid hormone content of the blood *and tissues such* as is occasioned by extirpation of an adreno-cortical tumor, is likely to produce a transitory corticoid deficiency Hence, the same preoperative measures (corticoid and NaCl treatment) are recommended as with orthotopic cortical neoplasms.

TESTOID HYPERTHECOSIS AND LEYDIG CELL TUMORS OF THE OVARY

Experimental work and clinical case reports indicate that hyperplasia and hypertrophy of luteinized theca cells can cause a type of virilism which has hitherto not been clearly recognized as a special disease entity. *Stein et al.* (1935-9) in their study of the "polycystic ovary" incidentally mention that



Tubular adenoma. At high magnification note absence of tubular lumina and resemblance to tubular granulosa-cell tumor (Courtesy of Dr P. Masson)

ing between growths which are "masculine" because of testoid production and those which morphologically imitate the male gonad. Other investigators regard all clinically masculinizing tumors as arrhenoblastomas irrespective of their histologic structure. Such definitions are confusing, since they group together a number of essentially different tumors (e.g., tubular adenomas, lipid cell tumors, etc.).

Some authors strictly separate the tubular adenoma without virilization from the arrhenoblastoma, defining the latter as histologically similar to the former, but always associated with pseudohermaphroditic *traits*. This purely functional separation is likewise not acceptable, at least until much more is known about the pathologic physiology of these neoplasms. Such a distinction would be no more justifiable than the assumption that a struma ovarii, which produces Graves' disease, is a neoplasm essentially different from one which does not elaborate enough thyroid hormone to cause detectable signs of hyperthyroidism. It is quite possible that the degree of Leydig cell development within the tubular adenomas could account for the virilization seen in some cases, but this has not yet been proven.

Some of the rete adenomas appear to be merely a slight exaggeration of the normal "male" part of the ovary, while in other cases the tubular structures imitate testis tissue so closely that the ovaries, which contain it, were described as true ovotestes The difficulty of accurate differentiation is well illustrated by the fact that one of the famous relevant cases was first described as an ovotestis and only later reclassified as an arrhenoblastoma.

The "false seminoma" or dysgerminoma, is listed as a separate blastoma type because its characteristic morphologic appearance clearly distinguishes it from the tubular adenoma.

CLASSIFICATION

According to their FUNCTION we distinguish between:

(1) *Virilizing tubular adenomas* (which usually contain Leydig cells).

(2) *Hormonally inert tubular adenomas.*

On a purely HISTOLOGIC BASIS we differentiate between:

(1) *Rete adenomas.*

(2) *Typical tubular adenomas.*

(3) *Partly tubular and partly diffuse adenomas.*

(4) *Entirely atypical tubular adenomas.*

(For their histologic characteristics, see: Pathologic Anatomy, below.)

PATHOLOGIC ANATOMY

Upon naked eye inspection, most tubular adenomas prove to be medium-sized, round, or ovoid solid growths. Their color as viewed from the surface is greyish-white, their consistency rather firm. On the cut surface, some of them (especially those containing many Leydig cells) are bright yellow.

The microscopic characteristics of the various types may be summarized as follows:

(1) RETE ADENOMAS consist mainly of rather regular, narrow tubules, localized in the rete region and resembling normal rete tubules. Such adenomas are comparatively common, usually of small size, and asymptomatic.

(2) TYPICAL TUBULAR ADENOMAS are often difficult to distinguish from the rete adenomas. They are claimed to originate, not from the rete tubules but from medullary cords, that is, structures corresponding to the seminiferous tubules of the testis. In these neoplasms, the stroma and the interstitial cells tend to be more developed than in the rete adenomas and they often reach a greater size. Frequently the epithelial components have no lumen and represent trabeculae rather than

quently atrophic, perhaps as part of the "virilization" syndrome.

INCIDENCE

Tubular adenomas are very rare. Among solid ovarian tumors, their incidence is approximately 1%.

They can occur at any age, but are most common in women between 20-35 years. In spite of their virilizing effect, they are compatible with pregnancy and tend to induce pseudohermaphroditic traits both in mother and offspring.

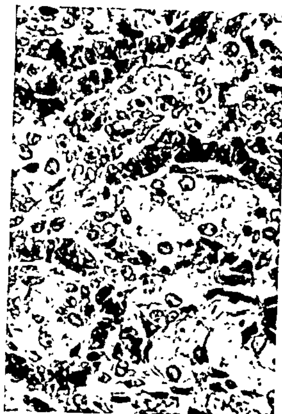
PATHOGENESIS

The striking resemblance of ovarian tubular adenomas to the corresponding testis tumors, their histologic structure, their frequent occurrence in the "male" hilus region of the ovary, and their ability to produce testoids, has led to the almost universal acceptance of the theory that they are derived from "MALE" GONADAL ELEMENTS IN THE OVARY. There are minor differences of opinion concerning the specific point of origin within this region. Some derive them from the rete, others from the medullary cords or even from the seminiferous tubules of a congenitally true-hermaphroditic gonad. The existence of intermediate types between dysgerminomas and tubular adenomas suggests close pathogenic correlations between these two "male" ovarian tumors.

In connection with such histogenetic considerations, surprisingly little attention has been given to the common occurrence of INTERSTITIAL CELLS within the stroma of tubular adenomas. These "Leydig cells" are strikingly similar to those found in the normal testis and in the hilus region of the normal ovary. In tubular adenomas, they can appear not only in the form of individual cell groups between tubules, but even as distinct lipid cell adenomas. Such cases may be regarded as intermediate between the pure (interstitial-cell-free) tubular adenomas and the pure Leydig cell tumors. (See: Testoid Hyperthecosis on p. 440.)

HEREDITARY FACTORS appear to play an important rôle in the causation of tubular adenomas, since they have repeatedly been observed in several members of the same family, or in combination with congenital malformations. It is probable, however, that even in hereditarily predisposed individuals, an additional growth impulse is necessary to elicit neoplastic proliferation in the ovary some time during post-embryonic life. Unlike "false seminomas" the tubular adenomas are rarely associated with congenital pseudohermaphroditism. Signs of mild virilism are common in normal women during pregnancy and after the menopause, when the ovarian rete tubules and Leydig cells tend to proliferate. The endocrine change responsible for "pseudohermaphroditic traits" during pregnancy and old age is still unknown, but it is rather tempting to look upon the virilizing tubular adenoma as an abnormal exaggeration of the same processes.

It is of interest in this connection that in female birds during embryonic life, treatment with TESTOID HORMONES can cause almost complete sex reversal with the development of functional seminiferous tubules, (see: Stimuli Influencing Ovary on p. 379). In mammalian embryos, such marked degrees of virilization cannot be obtained. However, during early post-embryonic life, overdosage with testoids causes pronounced inhibition in the development of the ovary, uterus and vagina, as well as adenomatous proliferation of the rete tubules. It is possible therefore that in women it is also a hormonal stimulus which elicits both the formation of "defeminizing and virilizing" tubular adenomas and the occasionally co-existent malformations of the Mullerian duct derivatives.



Arrhenoblastoma with Leydig cells? This tumor was originally described as a "luteinoma" (by Cosacesco et al) However, regions such as ... he trabecular ... ilar adenoma ... light) Leydig ...

(Courtesy of Dr P Masson)



Tubular adenoma. The tubular arrangement of epithelial cells is extremely indistinct in this neoplasm but large, epithelioid Leydig cells are clearly distinguishable among the narrow and irregular tubules

(Courtesy of Dr H-T Karsner)

tubules. A very large number of these neoplasms are distinctly virilizing.

(3) In ENTIRELY ATYPICAL TUBULAR ADENOMAS, the epithelial elements are so irregular that usually they cannot be distinguished with certainty and the diagnosis must rest partly upon the clinical manifestations of virilization. Many relevant cases have been mistaken for solid carcinomas or sarcomas of the ovary. Probably most, if not all ovarian solid carcinomas, carcinosarcomas, and sarcomas purported to have elicited signs of pseudohermaphroditism, actually belong to this group The same may be said about the malignant or carcinomatous tubular adenomas although, in some of these, tubular formations remain fairly distinct, at least in certain areas.

Transitional types between these main groups are common. Special emphasis must be laid upon the fact that in the case of group 3, the co-existence of diffusely arranged cells and tubulo-alveolar formations may give the growth an appearance very similar to that of granulosa cell tumors

The interstitial cells in the stroma of tubular adenomas are often in close contact with nerves. In this they resemble sympathicotropic cells of the normal ovary and the extra-testicular Leydig cells in the male

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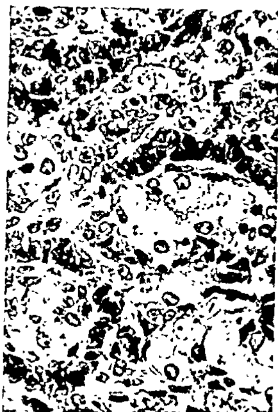
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(Courtesy of Dr P Masson)



Tubular adenoma. The tubular arrangement of epithelial cells is extremely indistinct in this neoplasm but large, epithelioid Leydig cells are clearly distinguishable among the narrow and irregular tubules.
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In cases of unilateral tubular adenomas, the contralateral ovary is fre-

Tubular adenomas can undergo carcinomatous transformation in which case the usual manifestations of an ovarian cancer are added to those of a virilizing neoplasm.

DIAGNOSIS

In the diagnosis of tubular adenomas, LOCAL SIGNS are rarely helpful, since these blastomas are usually of moderate size and exhibit no great tendency towards invasive growth. *Sometimes however, pelvic examination furnishes valuable data. If the tumor is virilizing, one should try to differentiate between ovarian and adrenal-cortical neoplasms and if there are no pseudohermaphroditic traits, the local signs may be the only detectable manifestations of the tubular adenoma.* Hence the preoperative diagnosis of these tumors is rarely possible. During the operation, the often (but not invariably) bright, yellow color of the cut surface can help the recognition of the neoplasm, but other virilizing tumors (especially the hypernephromas and Leydig cell tumors), as well as corpus luteum tumors and lipid-containing folliculomas may have the same color.

The signs of DEFEMINIZATION (*atrophy of breasts and uterus, amenorrhea, loss of libido, etc.*) and VIRILIZATION (hirsutism, growth of the clitoris, deepening of the voice, loss of scalp hair, *etc.) should always raise the suspicion* of a tubular adenoma. From a DIFFERENTIAL DIAGNOSTIC viewpoint, adren-

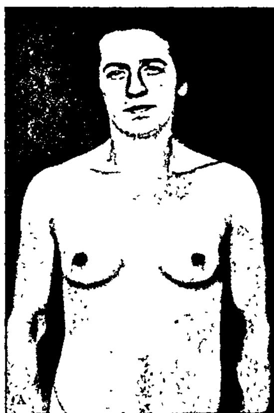


Virilization due to tubular adenoma. — A. *This 24-year-old patient suffered from amenorrhea* with an abdominal tumor, erroneously diagnosed as pregnancy Her *facial* expression became

[illegible]

but following ablation of her virilizing tumor The facial appearance of the patient became feminine again, the menses reappeared and two years after ablation of the tumor, she became pregnant She is shown here with her child

(After E Strassman Ztschr, f Geburtsh u Gynäk 99 368, 1938)





Virilization due to lipid-cell tumor *(hypernephroma ?)*. — A. Note masculine facial expression and body build, atrophy of breasts, excessive hair growth on abdomen and arms. The 32-year-old patient suffered from secondary amenorrhea, polycythemia (6,660,000 erythrocytes), slight hypertension, slight hyperglycemia and excessive development of the clitoris. She lost much of her scalp hair, especially in the temporal region but grew a light beard. After removal of a unilateral, lipid-cell tumor (interpreted as a lutein-cell tumor), the menses returned and all other symptoms and signs disappeared. — B. Same patient as that shown in Fig. A. Note acne, beard growth, slight temporal baldness and resemblance to patient on p. 447.
(After J. Novak and O. Wallis. Arch. f. Gynäk. *164*, 543, 1937.)

CLINICAL COURSE

In the majority of women with tubular adenomas of the ovary, LOCAL SIGNS are not particularly prominent (see: "Diagnosis" below).

The most striking manifestations of these neoplasms are due to the production of excessive quantities of testoid hormones, so that in the so-called "silent" varieties of these tumors, there are no characteristic clinical features. The sexual development and menstrual cycles are usually normal until the beginning of the illness when VIRILIZATION and DEFEMINIZATION become conspicuous. Gradually, there appears excessive hair growth on the upper lip chin, arms, legs and buttocks; the scalp hair tends to fall out, so that these bald women resemble middle-aged men. Acne may appear, the voice assumes a low pitch and is often hoarse, the clitoris is enlarged, there is amenorrhea and the uterus as well as the breasts, become atrophic. There is often a marked loss of libido. Usually neither the blood pressure nor the blood count show any conspicuous change, but in some cases there is a definite tendency to put on weight as the tumor develops.

Whether tubular adenomas can be the cause of METRORRHAGIAS is somewhat doubtful. Seemingly pertinent cases could belong to the granulosa cell group.

OVARIAN FALSE SEMINOMAS (DYSGERMINOMAS) OR EMBRYONIC CARCINOMAS OF THE OVARY

DEFINITION

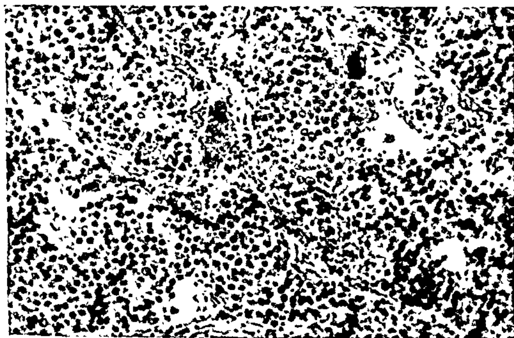
The false seminoma of the ovary is a malignant neoplasm characterized by the presence of medium-sized, round or polyhedral, lightly-staining cells, diffusely arranged in a loose stroma. The epithelial elements sometimes contain large amounts of glycogen and tend to form multinuclear giant-cells; the stroma is infiltrated with lymphocytes. This tumor often develops in children and in already pseudohermaphroditic individuals. Histologically, it strikingly resembles the false seminomas of the testis, but tends to be less malignant. It is not known to produce any hormones or obvious endocrine disturbances, although it can cause increased urinary elimination of gonadotrophins.

PATHOLOGIC ANATOMY

Seminomas are yellowish-grey, often encapsulated tumors of moderate size. They may cause death due to metastases, before the primary tumor reaches extensive proportions. On the cut surface, they exhibit a testis-like appearance About 35% of them are bilateral.

The microscopic appearance of the seminomas has been briefly outlined above in connection with their definition Contrary to common belief, they are not large-cellular cancers, since the average diameter of the epithelial cells usually varies between 12-18μ.

They often contain polynuclear giant cells which have been mistaken for the Langhans cells of tubercles These



False Seminoma. Note lymphocytic infiltration, in the connective tissue septa, between the epithelial cells (Courtesy of Dr P Masson)



Virilization caused by arrhenoblastoma. 66-year-old woman with *marked virilization. Note pronounced beard growth, baldness and coarse,* masculine facial expression. The ovary contained a partly tubular, partly papillary tumor with occasional giant cells. The tubular portion resembled the common, tubular adenoma but the neoplasm was not very typical.
(After A. Buttner, Virchow's Arch f Path Anat 289, 452, 1933.)

al-cortical tumors (of the adrenal itself or of adrenal-rests in the ovary) and Cushing's disease can often be excluded, *since in most tubular adenomas,* there is no special tendency towards the development of plethora, hypertension, diabetes, abdominal striae or the characteristic "moon face." However, a search for specific local signs in the adrenal and pituitary region is always indicated in such cases.

Urinary HORMONE DETERMINATIONS (17-KS, folliculoids or gonadotrophins) *have not been carried out in a sufficiently* large number of cases to be of real diagnostic value. The few reported data do not reveal any great deviation from the normal.

PROGNOSIS

The prognosis of tubular adenomas *is favorable, if the* tumors are completely removed. Since these neoplasms tend to occur in young women, *before or during the child-bearing* period, and since they are usually not malignant or bilateral, conservative operations are justified. Following removal of the growth, the menstrual cycles tend to reappear in previously amenorrheic patients, while most of the pseudohermaphroditic traits disappear. The loss of the excessive body and facial hair is particularly striking and becomes *noticeable a few weeks after* the operation. The libido also tends to return within a short period, and the *previously atrophic breasts* become full again. The enlarged clitoris usually regresses more slowly and some *virilization may persist.*

After the tumor is removed and the patient "refeminized," normal pregnancies occur in a fairly large number of cases.

Recurrences after the operation are comparatively rare, since most of these *tumors are benign* or of a low-grade malignancy.

THERAPY

The therapy of choice is the surgical removal of the tubular adenomas. No data are available concerning the efficacy of X-ray therapy and in view of the excellent results obtained by conservative surgery, experimentation along these lines is hardly justified.

In exceptional cases, *following removal of the (usually atrophic) ovary* containing the tubular adenoma, *severe menopause-like deficiency symptoms* are noted. This could be due to withdrawal of the hormones produced by the tumor itself and should be treated with folliculoids in the usual manner

which *frequently* shows malignant properties and tends to develop in young or pseudohermaphroditic individuals.

Women with false seminomas usually *exhibit pseudohermaphroditic traits* or genital hypoplasia from birth, or at least a long time before the neoplasm is noted (unlike patients with virilizing, testoid-hormone-producing ovarian tumors).

DIAGNOSIS

The preoperative diagnosis of ovarian false seminomas is next to impossible. The only *clinical signs* which may justify the suspicion of this tumor are its tendency to develop at an early age and often in individuals with marked signs of genital hypoplasia or *pseudohermaphroditism.*

False seminomas tend to be mobile and rarely become adherent to the adjacent tissues until late in their development. The frequently rapid growth *rate of the neoplasm can be verified* by repeated palpation, but none of these physical criteria are very characteristic. The use of lipiodol to obtain a good X-ray picture of the internal *sex organs may be of some value, especially* in recognizing associated abnormalities in the Müllerian derivatives.

Bioassays sometimes reveal increased gonadotrophin elimination, but the pertinent results are contradictory.

PROGNOSIS

False seminomas are rapidly-growing-tumors: they can fill the whole pelvis a few months after being barely detectable by palpation. Although some of them are benign, in most cases, their progress is rapid and lethal.

THERAPY

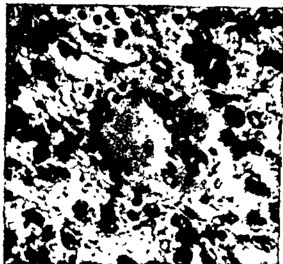
With ovarian false seminomas, the therapy of choice is complete SURGICAL removal of the ovaries and adnexa, combined with panhysterectomy. The frequency of recurrence is too great to warrant conservative interventions. This is true not only of large infiltrating false seminomas, but even of apparently circumscribed growths, especially if the patients are pseudohermaphrodites or if they suffer from malformations of the internal sex organs which are incompatible with normal reproduction. Yet in a fairly large number of patients, conservative removal of the tumor (leaving the contralateral ovary with the uterus and tube intact) has corrected previously existing menstrual anomalies. Hence unilateral ovariectomy may be considered if the neoplasm is very small and the accessory sex organs not severely deformed. In each case the risk entailed must be weighed against the desirability of maintaining the function of the contralateral gonad.

The great X-RAY sensitivity of the testicular false seminomas is apparently shared by the corresponding ovarian tumors. Under the influence of deep X-ray treatment, these tumors simply melt away and huge growths can almost disappear within a short time. With inoperable false seminomas, especially if they have produced widespread *metastases, roentgen therapy* is therefore the treatment of choice. It also has its place following surgical removal of the neoplasms as a prophylactic measure against recurrences. However, *in spite of the usually impressive* initial results, the neoplasms tend to become X-ray resistant and recur after some time.

STRUMA OVARII

DEFINITION

The struma ovarii is an ovarian teratoid which consists exclusively, or at least predominantly, of thyroid tissue. It can resemble the normal thyroid or the various forms of goiter:



Dysgerminoma giant cell. Note structure of *typical large giant cell*. There are several entirely independent nuclei. The outlines of the cytoplasm are indistinct and merge with the surroundings. A few lymphocytes appear to be engulfed by the giant cell

(Courtesy of Dr L. Berger)

gave rise to much speculation concerning a possible causal relationship between tuberculosis and seminoma formation. They have also been claimed to represent the same type of giant cell which is formed from normal seminiferous epithelium, under the influence of various damaging agents. A possible relationship with placental giant-cells must also be considered

The lymphocytic infiltration of the stroma (mentioned above) is one of the most characteristic features of seminomas.

Metastases are infrequent, but can occur in almost any organ

INCIDENCE

False seminomas are rare They hardly represent more than 1-2% of all solid ovarian tumors. They may occur at any age, but are most common during the second decade of life Their incidence in pregnancy is comparatively high.

PATHOGENESIS

The false seminomas have been claimed to develop from *remnants of the medulla* of the embryonic ovary. The extra-ovarian false seminomas, which are apparently incompatible with this theory, have been derived from undifferentiated ectopic gonadal parenchyme.

Another theory *holds that these* growths arise from abnormal *placental Langhans cells*, which tend to form syncytia. This interpretation is consonant with the increased gonadotrophin production of some false-seminoma-bearers.

The attempted derivation of these cells from the *Langhans cells* of *tubercles* is entirely unfounded.

Hereditary factors certainly have an important part in the pathogenesis of false seminomas. They frequently occur in sisters, in true hermaphrodites, and in conjunction with other congenital malformations. The often pronounced hypoplasia of the female accessory sex organs (e.g., uterus, vagina, breasts) may also be interpreted as due to a hereditary stigmatization. In some cases, there is even a complete or partial aplasia of Mullerian duct derivatives.

CLINICAL COURSE

False seminomas cause no typical endocrine disorder but they frequently occur in pseudohermaphrodites and in women with genital hypoplasia (see: Pathogenesis). Humoral *influences* probably play a rôle in the pathogenesis of these associated sexual manifestations.

In cases with pronounced uterine hypoplasia or aplasia, there is primary AMENORRHEA. In a large number of patients, the menstrual periods remain normal and pregnancy may occur.

In general, it can be said that the clinical course is notably devoid of any specific characteristics other than those due to the presence of an unusually rapidly growing, ovarian neoplasm

is sensitive to the same stimuli which influence normal thyroid tissue. In some cases, the cervical thyroid became enlarged and toxic after removal of a struma ovarii. These observations suggest close (hormonal?) correlations between orthotopic and ectopic thyroids.

CLINICAL COURSE

Usually the symptomatology of struma ovarii does not differ from that of other ovarian teratoids, unless there is hyperthyroidism. Quite frequently, however, they produce ASCITES.

Manifestations of severe THYROTOXICOSIS, such as an increased B.M.R., tremor and tachycardia have been noted in about 5-6% of all struma ovarii cases. After ovariectomy, the thyrotoxicosis subsided.

DIAGNOSIS

The clinical diagnosis of struma ovarii is usually impossible if there is no hyperthyroidism. If however, an ovarian tumor (especially a dermoid) appears in a woman who suffers from Graves' disease and yet has a normal thyroid, the diagnosis of struma ovarii must be considered. It is well to remember, furthermore, that several of the ovarian strumas which caused Graves' disease, developed in patients whose cervical thyroid also became toxic. In these, removal of the cervical thyroid produced but temporary improvement and final cure followed only after subsequent removal of the ovarian struma.

THERAPY

The therapy of choice in all cases of struma ovarii is REMOVAL OF THE GROWTH and this almost invariably necessitates complete ablation of the gonad itself. In view of the ever present danger of malignant or toxic transformation in ovarian thyroid tissue, conservative measures and delay are to be avoided.

OVARIAN CHORIONEPITHELIOMAS (CHORIONCARCINOMAS)

DEFINITION

The chorionepithelioma of the ovary is a carcinoma characterized by its great morphologic and functional resemblance to placental tissue. Its characteristics are

(1) The tumor is composed of both syncytium and Langhans cells These are arranged in masses or cords with Langhans cells inside and the syncytium peripherally

(2) The tumor has no connective tissue stroma or vascular supply of its own, but its cells surround and penetrate maternal blood vessels.

(3) There is coagulation of tissue, hemorrhage and necrosis

CLASSIFICATION

The chorionepitheliomas of the ovary are usually classified on the basis of their PATHOGENESIS as follows ·

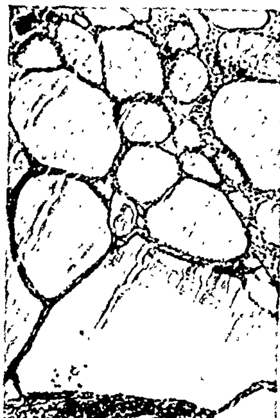
(1) OVARIAN CHORIONEPITHELIOMAS RESULTING FROM PREGNANCY.

(a) *From an ovarian pregnancy.*

(b) From a chorionepithelioma of the uterus which developed following pregnancy. In such cases, the original uterine tumor may be aborted before the ovarian neoplasm is noticed, thus rendering it difficult to recognize the secondary nature of the ovarian growth A secondary chorionepithelioma may also arise from an ectopic pregnancy in the oviduct or the pelvic peritoneum

(2) OVARIAN CHORIONEPITHELIOMAS WHICH ARE TERATOID TUMORS with one-sided development of chorionic elements, sometimes to the exclusion of other tissues

(3) PRIMARY "COMMON" OVARIAN CARCINOMAS WITH TROPHOBLAST-LIKE PROLIFERATIONS. It is doubtful whether these should be listed as a subdivision



Struma ovarii. Typical ovarian-thyroid tumor *containing no other tissue* This field illustrates a macrofollicular region
(Courtesy of Dr T R Waugh)

in some instances, it undergoes malignant transformation Because of its *potentially* endocrine nature and histologic uniformity, this growth is discussed separately from other teratoids It will be kept in mind, however, that small nodules of thyroid tissue can appear in any teratoid although usually their size is approximately in proportion to that of the other organs in the embryoma

PATHOLOGIC ANATOMY

Macroscopically, the struma ovarii is usually an irregularly-shaped, nodular, brownish growth The cut surface is honey-combed by numerous small follicles, sometimes even by large cystic cavities filled with colloid

Microscopically, the growth consists of colloid-containing follicles, or tubules and trabeculae similar to those in diffuse or nodular micro- or macrocystic cervical goiters.

It has been emphasized, however, that not all the colloid-containing ovarian growths which resemble goiter tissue are actually derived from a thyroid primordium. Some so-called "thyroid tumors" of the literature, greatly resemble ordinary cystadenomas Hence it has even been claimed that all these tumors are merely modified papillary or pseudomucinous cystadenomas. This interpretation is untenable, especially because the struma ovarii may copy any type of the struma colli and does not give a positive mucicarmin reaction: *it contains iodine* and *thyroid hormone* and in this respect, also resembles thyroid tissue.

It is estimated that about 5% of the ovarian strumas become malignant.

INCIDENCE

Struma ovarii is a rare neoplasm, its general incidence among ovarian teratomas being about 2.7%. Small, organoid thyroid inclusions however are detectable in about 10% of all ovarian embryomas.

Struma ovarii is about equally frequent at any age

PATHOGENESIS

The true thyroid nature of these growths appears to be well established. Histologically, especially with regard to their staining reactions, and chemically, with regard to their iodine and thyroid hormone content, these growths resemble thyroid tissue. As we shall see below they may even produce clinical manifestations of Graves' disease. It remains to be explained however, why thyroid tissue develops and even predominates in so many ovarian teratoids.

Cases in which both the cervical and the ovarian struma became toxic (see below) indicate that the ectopic thyroid

growths originating in the ovary, either from the chorionic villi of an ovarian pregnancy, or from the teratomatous transformation of a parthenogenetic ovum in which chorionic elements grow to the partial or complete exclusion of all other tissues. In support of this view, it has been emphasized that in the guinea-pig, chorionepithelioma-like structures appear to arise from parthenogenetically developing ova. Chorionepitheliomas in prepubertal children and virgins show that this neoplasm can develop without a foregoing pregnancy.

CLINICAL COURSE AND COMPLICATIONS

Apart from the non-specific local manifestations of a rapidly growing malignant ovarian tumor, the clinical course of chorionepitheliomas is not very characteristic. In some cases, irregular and prolonged UTERINE HEMORRHAGES call attention to a possible endocrine disturbance, but since so often chorionepitheliomas develop following normal or ectopic pregnancy, the vaginal bleeding is usually ascribed to placental remnants.

In children, *signs* of PRECOCIOUS PUBERTY such as precocious menstruation and breast development, often result from the abnormal production of gonadotrophic and folliculoid hormones by the neoplastic, chorionic tissue.

In adult women, PREGNANCY CHANGES (e.g., secretion of colostrum, discoloration of the vaginal mucosa and enlargement of the uterus) ensue, due to hormones produced directly by the tumor, or by the corpus luteum cysts which are secondarily formed under the influence of the excess chorionic gonadotrophins

The most important complications of chorionepitheliomas are hemorrhages from this highly vascular neoplasm or infiltration into adjacent organs, as well as metastases into distant structures.

DIAGNOSIS

The diagnosis of chorionepitheliomas is mainly based upon the local signs of an ovarian tumor in combination with evidence of excess sex-hormone production. The urine usually contains large amounts of chorionic gonadotrophin (LH) and folliculoids. However, *urinary bioassays do not permit differentiation with certainty* of the chorionepithelioma from hydatidiform moles and normal or ectopic gestation.

Unless *pregnancy can* be excluded with certainty, as in prepubertal children and virgins, ovarian chorionepitheliomas are clinically often indistinguishable from tubal or ovarian gestations. Since all these conditions require immediate surgical attention, such diagnostic errors are without serious consequences for the patient.

PROGNOSIS AND THERAPY

The PROGNOSIS of ovarian chorionepitheliomas is extremely grave, since this tumor is very malignant. Unless the neoplasm is surgically removed before it produces metastases, the outcome is invariably fatal within a short time. Even *after radical surgical* removal, fatal metastases and recurrences are common. The urinary gonadotrophin titer should always be checked repeatedly following the operation, since it is a good indicator of the continued presence of chorionepithelioma cells

The THERAPY of choice is early radicle removal, followed by deep X-ray treatment, but even patients so treated can rarely be saved.



Chorionepithelioma. — A. Part of a primary chorionepithelioma of the ovary. Note Langhans cells, bordered by large syncytial masses forming a villus — B. Another region of the primary ovarian chorionepithelioma shown in Fig. A. Note perivascular decidual cells in the ovary.
(Courtesy of Dr L-C Simard)

of the true ovarian chorionepitheliomas, although some prominent investigators regard it as such.

PATHOLOGIC ANATOMY

The outstanding macroscopic characteristics of chorionepitheliomas are their red color and brittle or spongy texture. Their microscopic features have already been enumerated in connection with the definition of these neoplasms.

It is noteworthy that the contralateral ovary may be transformed into a mass of cystic corpora lutea, probably as a result of the excess gonadotrophin formed by the neoplastic cells.

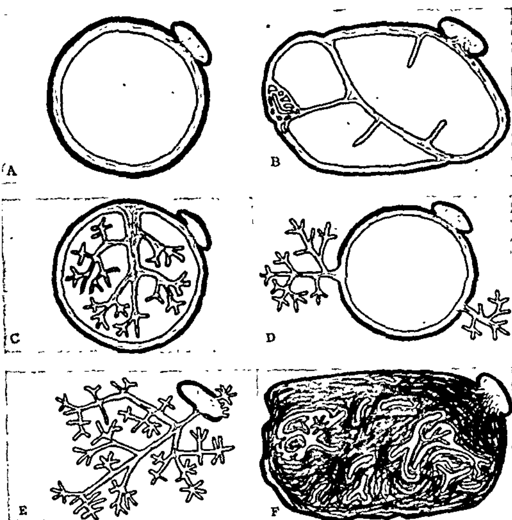
Since chorionepitheliomas are highly malignant, they tend to produce numerous metastases in various organs and to invade adjacent structures.

INCIDENCE

If secondary ovarian chorionepitheliomas are excluded, this is probably one of the rarest ovarian neoplasms. It tends to occur with approximately equal frequency in all age groups

PATHOGENESIS

lined in the part dealing with the classification of these tumors. There is, apparently, no single pathogenic mechanism which could explain all relevant cases Some are evidently primary



tumor type is always serous, never pseudomucinous
(After H Selye Ovarian Tumors Encyclopedia of Endocrinology 1946)

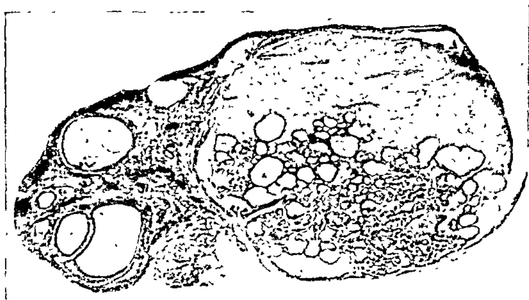
OVARIAN COMMON CYSTS

The common cysts of the ovary are of *great practical importance for the* gynecologist, but of comparatively little endocrinologic interest. They are not known to produce any specific hormones, nor is their development conditioned by endocrine stimuli. We mention them here only because they affect an endocrine gland, the ovary.

Most current CLASSIFICATIONS distinguish between the serous and the pseudomucinous ovarian cystomas, on the basis of the epithelium which lines *the individual cyst cavities.* The *serous* cysts or cystomas are lined by a low, cuboidal, or flattened epithelium, which produces a watery secretion The pseudomucinous cystomas, on the other *hand, possess high columnar* "pseudomucin"-producing lining cells, similar to those of the large intestine. Hence, their cavities are filled by a viscous *mucin-like secretion. Both these types* can be further subdivided according to the presence of various papillary excrescences in their cavity or on the outer cyst surface.

Little is known about the PATHOGENESIS of these neoplasms, but they are probably formed from embryonic remnants.

Their CLINICAL COURSE is not characterized by any endocrinologic abnormality. They rarely destroy the ovary *sufficiently to cause* signs of ovarian deficiency. They are important mainly because of the disturbances caused by their physical presence in the abdomen, and the ever-existing possibility of their *malignant transformation.* Some of the largest tumors occurring in man belong to this group.



Internal, racemose, serous papilloma. Left side of field is occupied by normal ovarian tissue with follicles On the right side there is a *little, serous, unilocular cystoma from* whose inner surface a racemose, small papilloma arises near the ovarian attachment. Note that each papillary excrescence is transformed into a grape-like structure (Very low magnification) (Courtesy of Dr L Berger)



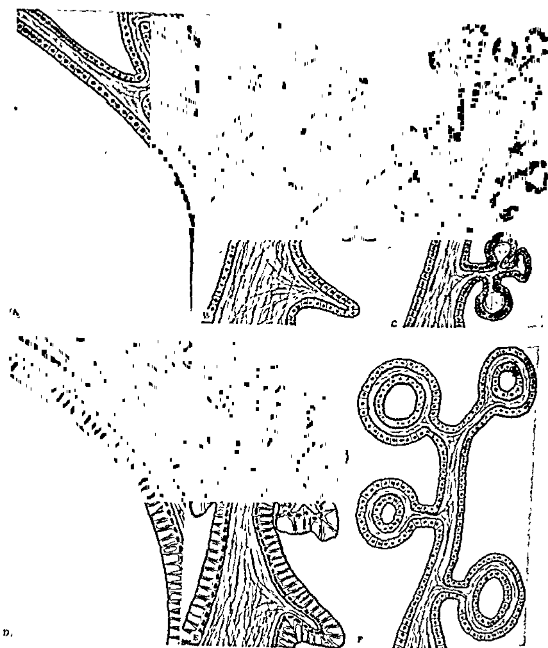
Large ovarian cyst causing cachexia.
Note enormous enlargement of the abdomen, dilatation of veins in abdominal wall, marked cachexia and characteristic "facies ovariana"
(After G Winter Lehrbuch der Gynäkologischen Diagnostik. Leipzig. 1897)



Multilocular pseudomucinous cystoma.
At low magnification note numerous independent cyst cavities filled by pseudomucinous fluid The partitions between some of the cysts are incomplete Papillomatous excrescences are noticeable on their surface
(Courtesy of Dr L. Berger)



Pseudomucinous papilliferous cystoma. Typically pseudomucinous lining with pseudomucin strands and cast-off cell debris between excrescences
(After H Selye "Ovarian Tumors" Encyclopedia of Endocrinology 1946)



by virtue of the fact that each "grape" actually contains a separate cyst cavity lined by the same type of serous epithelium which also covers the surface of the papillæ

(After H Selye "Ovarian Tumors" Encyclopedia of Endocrinology 1946)

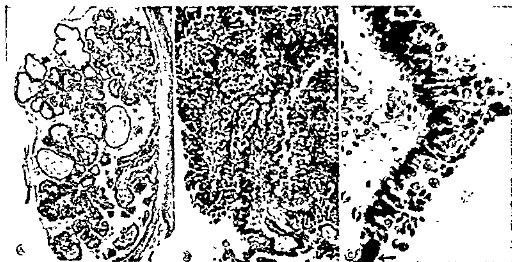
OVARIAN COMMON CARCINOMAS

The common carcinomas — as the common cystomas — of the ovary are of little endocrinologic interest. They produce no hormones, nor are they due to endocrine abnormalities. However, they can completely destroy the gonad, causing signs of ovarian failure. In gynecology, the ovarian carcinomas are of great importance because of their comparative frequency and often great malignancy.

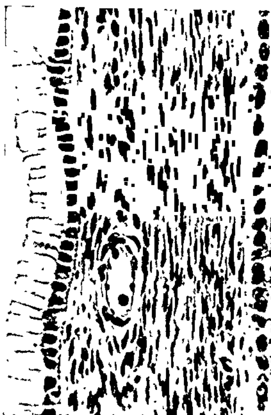
Most of the cystic PRIMARY OVARIAN CARCINOMAS are due to malignant transformation of originally benign cystomas. Correspondingly, we distinguish serous and pseudomucinous cystic ovarian carcinomas. A comparatively small percentage of the primary ovarian cancers are solid and these are probably due to direct malignant transformation of epithelial ovarian components.

The ovary is also frequently the site of SECONDARY CARCINOMAS which may affect it by direct infiltration from adjacent organs, or due to deposition of metastatic tumor foci. Among the metastatic ovarian cancers, the so-called *Krukenberg tumors* are of special interest. These are characterized by typical "signet ring cells" which contain some mucous material. They are almost always bilateral and secondary to a mucous carcinoma of the gastrointestinal tract, usually the stomach

The CLINICAL COURSE of ovarian carcinomas is chiefly dependent upon the rate of spread into adjacent organs, metastases, and in the case of secondary ovarian cancers, the progress of the primary neoplasm.



Serous, papillary carcinoma. — A. Small papillary excrescences on inner surface of a cyst wall. In this region, the tumor is remarkably typical — B. Higher magnification of a region in the tumor shown in Fig A The invasive growth of the epithelium is clearly visible at this magnification — C. A small field in the tumor shown in Figs A and B Note the regular and typical appearance of a few cells lining this excrescence (marked by arrow) The remainder of the lining is stratified, irregular and definitely of a malignant character The shape and size of the nuclei are very irregular (Oil immersion) (Courtesy of Dr L Berger)





Pseudomucinous cystoma. Septum illustrating marked differences which may occur in the epithelium of two adjacent cavities Cavity on left lined by cylindric epithelium containing practically no pseudomucin on right high cylindric pseudomucinous covering
(Courtesy of Dr P Masson)

Argentaffin cells in a pseudomucinous cystoma. Note the numerous argentaffin granules around and below the nucleus of one pseudomucinous cell (marked by arrow) (Courtesy of Dr P Masson)

OVARIAN MESONEPHROMAS

The term "mesonephroma" is applied to ovarian tumors which resemble the embryonic mesonephros and have the following characteristics: (1) a glomerulus-like unit, consisting of a small cystic cavity which contains one capillary loop covered with columnar epithelial cells, whereas the cavity is lined with low endothelium-like cells: (2) solid areas consisting of proliferating, stellate endothelial cells, connected with each other by fine filiform projections. These two specific structures are definitely free from mucin. Limited production of a mucinous secretion is occasionally found in the small cystic cavities, but the "mesonephroma" never shows mucinous secretion comparable to that of the pseudomucinous cystomas. The tumor may be benign or malignant.

Schiller (1939) who originally described this tumor, considered it as a special neoplastic entity but many pathologists doubt its mesonephric origin and regard it merely as one of the types of serous cystomas, or of teratoids. (See also: Teratoids of Testis.)

BRENNER TUMORS OR BRENNEROMAS

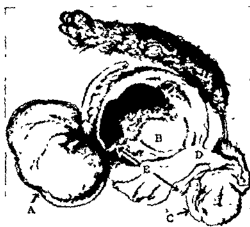
The Brenner tumor is a benign, partly fibrous and partly epithelial growth of the ovary. The relative proportions of epithelial and stroma tissue are extremely variable, but quite frequently the latter prevails. The epithelial component consists of solid or cystic aggregations of cells, not unlike those seen in the basal layers of stratified-squamous surface epithelia. If cystic cavities are formed, the innermost lining cells tend to produce pseudomucin.

They are comparatively rare neoplasms without known endocrinologic significance.

TERATOID TUMORS (DERMOIDS, SOLID TERATOMAS, EMBRYOMAS)

TERATOMAS are growths composed of tissues and organs of one, two or three germinal layers (monodermal, bidermal or tridermal types) The EMBRYOMA is composed of tissues derived from all three germinal layers, in more or less orderly imitation of a fetus These growths differ therefore from simple, MIXED TUMORS which are composed of more than one type of irregularly arranged neoplastic tissue, named according to composition (e.g., "chondro-epithelioma," "osteo-chondro-myosarcoma") In the sense of these definitions, both the cystic and solid teratoid tumors of the ovary are teratomas. The DERMOID CYST deserves special consideration only because of its frequency

Except when, in a complex embryoma one or the other endocrine tissue (e g., thyroid, adrenal cortex) develops

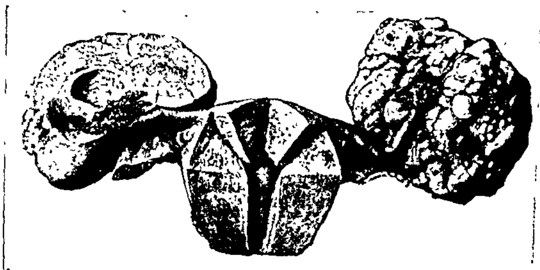


Dermoid cyst with an almost completely formed [illegible]

(After G Kaboth Arch f Gynak 122 803 1924)

Adenocarcinoma. Purely gland-like solid carcinoma of the ovary.
(Courtesy of Dr R.-T Waugh)

Krukenberg tumor. Signet-ring cells and one bi-nucleated giant cell in a Krukenberg tumor with a comparatively loose cell arrangement (as seen under very high magnification).
(After H Selye "Ovarian Tumors" Encyclopedia of Endocrinology, 1946)



Gross appearance of a bilateral Krukenberg tumor together with the tubes and uterus. Note solid, nodular appearance characteristic of these tumors which are usually secondary to a carcinoma of the gastrointestinal tract.
(After E Novak Textbook of Gynecology William & Wilkins 1944)

sufficiently to cause overdosage manifestations, the ovarian teratoids are of no endocrinologic importance. Hence we shall not discuss them here in detail.

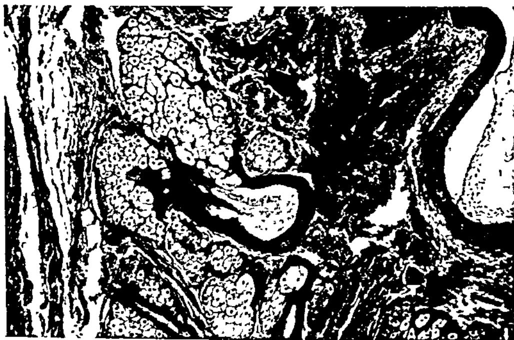
From a PATHOGENETIC point of view it is interesting, however, that the ovarian teratoids have variously been derived from parthenogenetic (unfertilized) ova, or from blastomeres separated from the rest of the fetal body at an early stage of embryonic development. It has also been assumed that teratoma formation is due to failure of the individuation field at an early period in embryonic development or to an interference with the normal effect of the embryonic "organizer," resulting in the formation of secondary embryonic axes in the primitive shield.

OVARIAN NERVE TUMORS, such as ganglioneuromas or gangliocytoneuromas, are also interpreted as abnormal, one-sidedly developed teratoids.



X-ray appearance of dermoid teeth. X-ray taken especially to illustrate structure of dermoid teeth. Note cluster of teeth, with well-defined root canals, in the vicinity of an ossified plaque on one side, and two less regularly formed teeth on the other side of the pelvis.

(Courtesy of Department of Radiology, Royal Victoria Hospital Montreal.)



Dermoid cyst. Typical skin-like area in the wall of a dermoid cyst. Note stratified, squamous epithelium lining the cyst cavity (right) and numerous sebaceous glands around hair follicles in the left part of the field. (Courtesy of Dr H.-T. Karsner.)





Dysembryoma. — A. Portion of a particularly polymorph, microcystic teratoid In this field a well-differentiated and regular intestinal wall is clearly distinguishable. Note numerous mucus-producing cells in intestinal crypts, lamina propria mucosæ and two layers of smooth
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(After H Selye Ovarian Tumors Encyclopedia of Endocrinology 1946)

NON-EPITHELIAL NEOPLASMS DEVOID OF ENDOCRINE FUNCTION

Since these tumors are of no endocrinologic interest, we shall merely enumerate them here :

FIBROMAS, are often bilateral and histologically resemble diffuse thecomas. For reasons which have not yet been fully clarified, they tend to be accompanied by ascites and pleural fluid accumulations (*Meig's syndrome*).

Various SARCOMAS (spindle and round cell sarcomas, myxosarcomas, melanosarcomas, lymphosarcomas, liposarcomas) and other mesodermal tumors may occur in the ovary; sometimes perhaps as a result of neoplastic transformation of misplaced embryonic remnants; at other times, due to secondary metastatic invasion of the gonad by tumor cells.

ENDOMETRIOSIS

DEFINITION

Endometriosis is a condition in which endometrial tissue proliferates in an ectopic location.

It is customary to distinguish between internal (direct) and external (indirect) endometriosis, depending upon whether the endometrial tissue proliferates within the uterus (by growing into the muscle directly from the inside), or whether it grows outside the uterus (on the surface of the uterus, oviduct or ovary, within the oviduct, in the pelvic peritoneum, the intestinal serosa, etc.).

The terms *internal*, direct, or primary endometriosis and adenomyosis uteri are synonymously used to denote endometriomas which develop in direct continuity with the endometrium and invade the uterus from the inside; the designations *external*, indirect, secondary, migratory or metastatic endometriosis are reserved for all other endometriomas. The name "endocervicosis" is sometimes used to describe "cervix erosions" with manifestly endometrial lining, while the designation "salpingitis isthmica nodosa" refers to endometriosis in the isthmus of the oviduct.

The ectopic endometrium may lead to cyst-formation and in this event, if menstruation occurs, the blood is usually retained within the cyst cavity and gives rise to the so-called "chocolate cysts" or "tarry cysts." The same designation has also been applied to hemorrhagic follicular or corpus luteum cysts, but the use of such non-committal terms is no longer justified since the characteristic lining permits the definite identification of endometriomas.

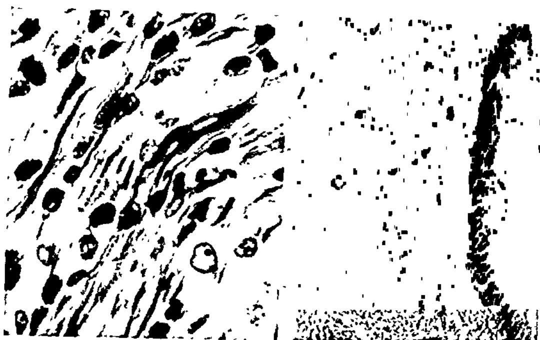
Endometriosis is not an endocrinologic disease inasmuch as the cells of an "endometrioma" (a focus of endometriosis) are not known to produce any hormones; however, the growth of endometriomas is definitely dependent upon stimulation by hormones. For this reason, and because of its great frequency, the process is of considerable endocrinologic interest. For the sake of simplicity, we shall discuss endometriosis of the ovary in conjunction with extra ovarian endometriosis.

CLASSIFICATION

The various types of endometriosis may be classified according to different viewpoints. Thus we may distinguish between the usual benign and the rare malignant endometriosis.

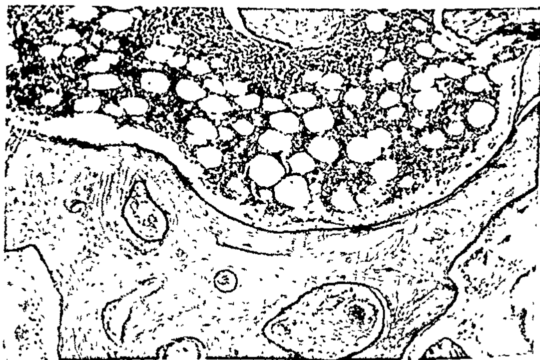
Goodall (1942) proposed the following classification in which endosalpingiosis and endocervicosis are also included

- Endometriosis
  - Mixed
    - Benign
    - Malignant
  - Stromatous
    - Benign
    - Malignant
- Endosalpingiosis
- Endocervicosis



Rhabdomyosarcoma of the ovary. One field in a typical rhabdomyosarcoma of the ovary showing bundles which consist of striated muscle fibrils. Note also polymorph nuclei, containing unusually large nucleoli. (Courtesy of Dr L. Berger.)

... Two ... n the ... The cells are entirely typical and differentiated, it is very doubtful whether such small ectopic tissue accumulations should be regarded as adenomas. (Courtesy of Dr L. Berger.)



Dermoid cyst. Apparently normal bone tissue with bone marrow are visible here within the cyst wall. (Courtesy of Dr H.-T. Karsner.)





Endometriosis of the ovary. — A. Low magnification of a section through the entire ovary. A large corpus luteum is visible in the right pole of the gonad and the entire surface is encircled by (light) endometrial tissue which underwent decidual transformation — B. High magnification of a field in the ovary shown in Fig A Note that here again the entire subcapsular region is transformed into decidua This case is especially instructive since in conjunction with Fig A, it demonstrates the transformation of the endometrioma under the influence of the corpus luteum tissue

(After H Selye Ovarian Tumors Encyclopedia of Endocrinology 1946)

PATHOLOGIC ANATOMY

MACROSCOPICALLY, endometriomas are usually small cystic masses surrounded by adhesions. Their cavity is filled with a "tarry" chocolate-colored fluid, containing partly decomposed blood-pigment. They form rather puckered, hemorrhagic, reddish or bluish areas on the uterosacral ligament, the anterior surface of the sigmoid and the rectum; not infrequently such endometriomatous areas are found diffusely throughout the pelvic peritoneum The diameter of endometriomas varies from a few mm to 5 or even 10 cm.

The comparative frequency of *endometriosis in different locations may be* estimated from the following statistical survey, comprising 307 patients, with external endometriosis and 343 major organ lesions (*Payne*, 1940)

Organs	% of Organs Involved
One ovary	36 0
Both ovaries	28 0
Cul-de-sac	25 0
Fallopian tubes	3 2
Tubal stumps	1 1
External surface of the uterus	2 0
Broad ligament	3 4
Rectovaginal septum	1 1
Umbilicus	1 1
Cervix	0 25
Appendix	0 25
Bladder	0 25
Laparotomy scar	0 25

MICROSCOPICALLY, the ectopic endometrial mucosa in endometriomas resembles the normal lining of the uterus



Internal endometriosis. Cross-section through *the uterus, showing the endometrium which lines* the cavity, and fairly large portions of the myometrium which are invaded by tubules and cysts of endometrial tissue One large endometrial cyst is visible in the lower, left corner of the field (X)
(Courtesy of Dr L Berger)



Endometrioma of the ovary. Among the several cystic cavities in this field one (X) is lined by a well-developed endometrium in which the glandular spaces are clearly distinguishable even at this low magnification
(After H Selye "Ovarian Tumors" Encyclopedia of Endocrinology, 1946)

It is debatable whether that type of endometriosis which happens to occur in the cervix uteri deserves a special designation instead of being described merely as "endometriosis of the cervix," in analogy with other localizations to which we simply refer as endometriosis of the rectum, sigmoid, etc. It is likewise questionable whether endosalpingiosis should be classified as a type of endometriosis

Obviously, it would also be possible to subdivide the various types purely on *the basis of the location of the endo-*metrioma into ovarian, tubal, uterine, diffuse pelvic, generalized peritoneal, etc. Such a purely topographic system of classification is of little practical use.



Blue dome cyst. Note characteristic appearance of small endometrial nodules on vaginal fornix These are called "blue dome cysts" because the menstrual blood, accumulating in the cystlets, gives them a bluish hue
(After W T Dannreuther Amer J Obstet and Gynec 41 461 1941)

furthermore that endometrial tissue can be transplanted without great difficulty, and that in its new location it remains sensitive to stimulation by ovarian hormones. In clinical medicine autotransplantation of endometrium is sometimes practised to re-establish menstruation following complete obliteration of the uterine lumen (transplantation into the artificially recanalized myometrium), after sub-total hysterectomy (transplantation into the cervical canal), or even after complete hysterectomy (transplantation into the vaginal fornix). This transplanted endometrium is comparable to a spontaneous endometrioma, and since it grows and functions as the latter does, there is no reason to doubt that endometriomas can result from heterotopic implantation.

The concept of *endosalpingiosis* also developed along the lines of the implantation theory. It was found that sometimes following tubal resections, islets of oviduct mucosa appear on the peritoneum. We are therefore probably dealing with a condition similar to endometriosis except for the fact that it is tubal, not uterine, mucosa tissue which implants itself in an atypical location. Since in some instances this tubal mucosa appears to have shown a tendency to transform itself into the endometrial type, it has been assumed that endosalpingiosis is only a modification of endometriosis.

Among other pathogenetic interpretations we might mention the LYMPHATIC DISSEMINATION THEORY, which assumes that endometrial tissue is reimplanted following migration through lymph channels. The HEMATOGENOUS DISSEMINATION THEORY postulates that endometrial particles are transplanted, like malignant tumor metastases, after migration through the blood stream The rare cases of endometriomas in the arms or lung could hardly be explained on the basis of any other assumption. The CELOMIC METAPLASIA THEORY holds that glandular tubules arise directly from the peritoneal mesothelium, perhaps under the influence of an irritating local inflammation. Finally, several theories assume that endometriomas develop from misplaced embryonic primordia.

Although most contemporary investigators subscribe to the direct transplantation theory, it is not impossible that endometriomas can also arise due to other pathogenetic mechanisms In any event, the endometriomas within the musculature of the uterus are certainly due to invasion from the endometrial lining.

As regards the FUNCTIONAL PATHOGENESIS of endometriomas, it appears that they are primarily due to endocrine disturbances. They are never observed in men nor in prepubertal or postmenopausal women, but they are particularly frequent in patients suffering from hyperfolliculoidism and invariably regress following castration.

Hormonal or other functional stimuli could promote the growth of endometriomatous tissue through diverse histogenetic mechanisms. Thus, folliculoids might enhance the regurgitation and implantation of endometrial tissue or its invasive tendencies, but they could conceivably also stimulate the metaplasia of celomic epithelium into endometrioid tissue, etc

Endometriosis tends to develop in abdominal scars, sometimes it is seen even after laparotomies which do not involve an endometrial trauma, for instance after appendectomy and panhysterectomy Its occurrence in the scar following interventions on the uterus, (e g , ceasarian section, laparotomy for ectopic pregnancy, or perforation of the uterus during induced abortion) find their most natural explanation in the assumption that uterine mucosa is accidentally transplanted into the abdominal wound during the intervention.

Endometriosis following endometrial or endosalpingeal trauma caused by

It usually responds to the same hormonal stimuli which regulate the development and menstrual shedding of the normal, orthotopic endometrium in the uterine cavity. As a result of repeated menstrual bleeding, the surface of the endometrioma — or the central cavity in the cystic variety of this growth — frequently contains menstrual blood. In cystic endometriomas, this blood tends to accumulate and distend the cyst, compressing its epithelial surface. As a result of secondary changes in the blood, its color becomes gradually darker with a brownish tinge, and its consistency thickens.

Owing to pressure by the accumulated menstrual blood, the surface lining can be completely destroyed so that the cysts are not lined by any surface covering. In such instances, the wall of the cyst consists merely of connective tissue *with numerous blood-pigment* containing macrophages. Sometimes these macrophages contain lipid material and then they are described as "PSEUDOXANTHOMA CELLS." If stroma cells predominate, we speak of "STROMATOUS ENDOMETRIOSIS."

The ectopic endometrial tissue can exhibit the usual histologic changes characteristic of the various phases of the uterine cycle and in the presence of an active corpus luteum (e.g., normal cycle or pregnancy) it can undergo the decidual type of PROGESTATIONAL PROLIFERATION.

The OVARIAN REMNANT and the CONTRALATERAL OVARY show no characteristic changes in patients with ovarian endometriomas Occasionally however they contain persistent follicles and these are also common in women in whom endometriomas develop outside the gonads

INCIDENCE

The GENERAL INCIDENCE of endometriosis is undoubtedly very high. It is estimated that about 20% of all women requiring abdominal operations for any cause suffer from endometriosis. The *disease is most common* during the child-bearing period of life. A survey of 260 patients who underwent operations for endometriosis can be summarized as follows *(Fallas and Rosenblum*, 1940) :

Years	% Internal	% External	% Combined
Less than 20	0.0	0.0	0.0
20-24	0.0	2.1	5.5
25-29	5.4	17.9	11.1
30-34	10.0	34.8	13.9
35-39	19.3	23.2	25.0
40-44	27.1	11.6	22.2
45-49	24.0	8.4	19.4
50-54	10.9	1.0	2.8
55-59	2.3	1.0	0.0
60-64	0.8	0.0	0.0
Over 60	0.0	0.0	0.0
Total No of cases	129	95	36

The PREGNANCY INCIDENCE of endometriosis is low because the disease is usually associated with sterility, and during gestation, women who previously suffered from endometriosis tend to become symptom-free because the ectopic endometrium — just as the normal uterine mucosa — does not undergo cyclic variations at this time.

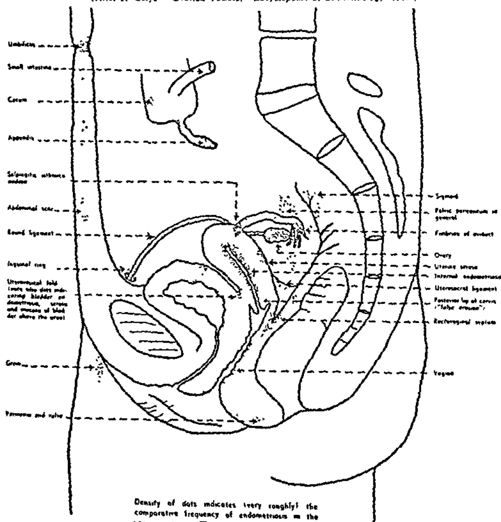
PATHOGENESIS

The most generally accepted histogenetic interpretation of endometriosis is the IMPLANTATION THEORY (Samson, 1921). It assumes that particles of uterine mucosa regurgitate through the Fallopian tubes into the peritoneal cavity at the time of menstruation and implant themselves there. The secondary foci grow, tend to become cystic and can in turn give rise to additional implantations by spreading endometrial particles upon the peritoneum subsequent to rupture of the cysts. The ovaries are usually, but not always, the first to be involved.

On the occasion of laparotomies during menstruation, it has been shown, *in support of this view*, that in fact, menstrual blood regurgitates through the oviducts into the pelvic cavity Numerous animal experiments indicate

uterine cancer. As previously stated however, there are no symptoms which could be regarded as pathognomonic of endometriosis, since the symptomatology in any particular case is so greatly dependent upon the position of the endometriomas, and very often this condition develops in conjunction with other disturbances (e.g., uterine fibroids, metropathia hemorrhagica and follicle cysts) which obscure the clinical picture. For this reason, a definite preoperative diagnosis is often impossible. However, it is justified to suspect endometriosis in the presence of such common and characteristic manifestations as acquired dysmenorrhea (especially the premenstrual and intramenstrual type) and menstrual pain referred to the rectum, the lower sacral or coccygeal regions, a constant "bearing down" sensation ("as if everything were falling out of the pelvis") or pain referred to the groins,

Distribution of endometriosis
(After H Selye 'Ovarian Tumors, Encyclopedia of Endocrinology 1946)



Density of dots indicates (very roughly) the comparative frequency of endometriosis in the various regions. The most exceptional localizations in ureter, lung, arm and lymph nodes are not represented in the drawing

utero-tubal insufflation or salpingectomy may be explained in a similar manner.

CLINICAL COURSE AND COMPLICATIONS

There is no symptomatology characteristic of this disease as such. Most of the patient's complaints are attributable to the direct action of the misplaced endometrial tissue and hence the special symptomatology in any one case depends principally upon the topography and extent of the endometriomas. Thus almost all the manifestations of the disease enter into the group usually considered as "complications."

The multiformity of the symptomatology of endometriosis is clearly shown by statistical surveys such as the following, in which the incidence of the CHIEF COMPLAINTS are listed (*Payne*, 1940)

Chief Complaints	%
Abnormal menstrual periods	56 0
Intermenstrual discomfort and pain	40 0
Dysmenorrhea	35 0
Backache	21 0
Dysfunction of contiguous organs	17 4
Pelvic tumor	12 5
Marital and fertility difficulties	6 6
Miscellaneous	7 5

It has been found that enlargement of the UTERUS with retroflexion or retroversion is particularly frequent in patients suffering from endometriosis Other uterine changes are also common, partly because the internal type of endometriosis is especially frequent and partly because these women are predisposed to uterine fibroids and metropathia hemorrhagica, probably due to a common hormonal etiology of these diseases.

Dysmenorrhea is another frequent symptom In a series of 80 histologically-confirmed cases of pelvic endometriosis, dysmenorrhea was the chief complaint in 66% of the patients (*Holmes*, 1942). The type of dysmenorrhea in this series is illustrated in the following table:

Type of Dysmenorrhea	%
Pre- and intramenstrual pain	25.0
Dysmenorrhea all of menstrual life	21 1
Acquired dysmenorrhea	11 2
Premenstrual pain	15.0
Postmenstrual pain	8 7
Normal periods	18 6

Endometriosis is usually accompanied by pre- and/or intramenstrual dysmenorrhea and the pain is rarely of the postmenstrual or intermenstrual ("Mittelschmerz") type.

The high incidence of STERILITY is probably due to several factors, such as concurrent metropathia hemorrhagica, uterine fibroids, persistent follicles, retrodisplacement of the uterus, dyspareunia, and a tendency for ectopic or otherwise abnormal gestations.

Massive invasion of the uterus can result in uterine rupture, especially during gestation or at the occasion of a curettage. Endometriosis of the oviduct ("salpingitis isthmica nodosa" or "endosalpingiosis of the cornua") probably arises from direct invasion of the muscularis by the mucosa of the oviduct itself, or by endometrium which invades the Fallopian tube through the isthmus. Such cornual lesions can sometimes be diagnosed preoperatively by uterosalpingography, but they are of little clinical significance, occasionally they cause sterility or a tendency toward ectopic implantation of fertilized ova

Endometriosis of the umbilicus can cause regular menstrual bleeding from the navel Such "supplementary" or "vicarious menstruation" has also been noted in endometriomas which developed following laparotomy

DIAGNOSIS

X-ray studies and biopsy often facilitate the recognition of internal endometriosis and its differentiation from

Only little is known, as yet, about the effectiveness of the HORMONE therapy of endometriosis. Progesterone and testoid hormones enjoy some popularity in connection with the treatment of dysmenorrhea due to unknown causes. Since testoids cause atrophy of the orthotopic endometrium, it is possible that such treatment alleviates dysmenorrhea, by virtue of this same effect upon the ectopic uterine mucosa.

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A monograph (12 pages, numerous illustrations and references) concerned with the morphology of the ovary in birds, with special reference to virilization following partial ovariectomy. (In French.)

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An encyclopedic treatise (1107 pages, numerous illustrations and references) concerning the rôle of hormones in gynecologic diseases. (In German)

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A monograph (312 pages, numerous excellent illustrations and a fairly complete review of the pertinent literature up to 1925) concerned with the technic and consequences of ovarian and testicular transplantation in intact and gonadectomized fowl. (In French)

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Three large, extensively illustrated, volumes with numerous references. The treatise is written mainly for practical gynecologists and obstetricians, it contains several chapters surveying the rôle of hormones in gynecology. This is one of the most complete encyclopedic treatises on this subject in the English language.

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A book (453 pages 169 illustrations and numerous references) concerned with the application of endocrinology to practical gynecology. This volume is somewhat superseded by the more recent book of the same author (see below) which covers approximately the same subject.

HAMBLEN, E. C. *Endocrinology of Woman.* Charles C Thomas, Publ., Springfield, Ill (1945).

hips and thighs. Dyspareunia is especially common in patients with endometriosis of the rectovaginal septum or the vagina. Nodular thickenings due to endometriomas in the uterosacral ligament or masses in Douglas' space can often be palpated from the vagina or rectum.

From the differential diagnostic point of view it is important to remember that endometriosis of the ovary can be confused with ovarian tumors, internal endometriosis with submucous uterine fibroids, pelvic endometriosis with chronic adnexitis, endometriosis of the intestine with carcinoma of the bowel and endometriosis of the urinary bladder with carcinomas or papillomas of the bladder. A ruptured ovarian endometrioma can present itself under the picture of acute peritonitis, ruptured ectopic pregnancy or acute appendicitis. However, if these possibilities of errors are envisaged they can usually be avoided

Untreated endometriosis is usually progressive although its progress is sometimes very slow Spontaneous regression or amelioration of the condition cannot be expected until the menopause, when the endometriomas become dormant due to cessation of ovarian function

Following surgical or X-ray therapy on the other hand, the prognosis is good There has been a great deal of discussion concerning the advisability of conservative versus radical surgery The manifestations invariably disappear after complete ovariectomy, while partial resection of the ovaries, or of individual endometriomas is frequently followed by recurrences. However, if all the visible endometriomas can be removed, the condition of the patient is often considerably improved and even permanent cures, and subsequent pregnancies, are possible

THERAPY

Conservative RESECTION of endometriomatous tissue frequently gives excellent results and is hence to be recommended, especially in the case of young women who are anxious to remain fertile. Frequently, small endometriomas remain symptomless and are only accidentally encountered by the surgeon in the course of operations for other reasons. In such instances, it is best merely to destroy the nodules with the cautery or to excise them. Even if one ovary contains a good deal of endometriomatous tissue, it is best to perform a unilateral ovariectomy if the patient is still young.

In older women, or if the endometriosis is very extensive and the uterus or adjacent organs (e g., intestine, bladder) are severely involved, it is best to remove the ovaries together with the uterus and the tubes, unless the patient insists on retaining her (generally slight) chance of becoming pregnant. It is unnecessary, however, even in the most severe cases, to practice extensive resections of adjacent organs (such as the rectum, sigmoid or bladder), since following complete ovariectomy, endometriomas in these organs tend to regress or at least remain dormant and symptomless

X-RAY OR RADIUM therapy is of value mainly as a means of temporary or permanent castration leading to secondary regression of the endometriomas Direct irradiation of the latter is rarely conducive to permanent cures, because for technical reasons it is usually impossible to reach all the abnormal tissue.

Since endometriosis frequently develops following surgical interventions and other types of trauma to the internal genital organs, an increasingly great emphasis is placed upon the PROPHYLAXIS of endometriosis by great care to prevent spreading the lining epithelium during such operations.

mainly from the chemist's point of view. Clinical implications are only touched upon.

PÉZARD, SAND ET CARIDROIT: *Les Hormones Sexuelles et le Gynandromorphisme chez les Gallinaces.* Imprimerie H. Vaillant-Carmanne, Liège (1926)

A classic monograph (105 pages, 81 excellent illustrations, 30 of them in color, numerous references to the older literature) reviewing the entire problem of intersexuality in birds, mainly on the basis of the authors' extensive experimental material (In French)

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An up-to-date synopsis (16 pages, 93 references) in which chemical, physical and biological assay methods are critically described.

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A book (463 pages, few illustrations, several hundred references) surveying the problem of experimental intersexuality as obtained in mice by the administration of folliculoid and testoid compounds during embryonic life. The treatise is mainly based upon the author's extensive personal investigations in this field (In French)

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A book (450 pages, 194 illustrations numerous references) surveying the causes, diagnosis and treatment of impaired fertility in women. A good deal of emphasis is placed upon the description of pertinent technics and their evaluation.

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A monograph (235 pages, 36 illustrations, 536 references) concerning the experimental production of tumors by chronic folliculoid treatment in animals. Largely based upon the author's personal investigations in this field. (In German.)

WHITE, CLIFFORD ET AL.: *Diseases of Women.* Edited by *Sir Comyns Berkeley,* C White and Frank Cook, 6th Ed, Edward Arnold & Co, Publ, London (1938).

A brief textbook (492 pages, 159 illustrations, *but no references) in which the rôle* of hormones receives comparatively little attention, but the volume represents an excellent, concise summary of the non-endocrine problems in gynecology.

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An excellent and detailed treatise (649 pages, 380 illustrations, numerous references) on hermaphroditism and pseudohermaphroditism This is perhaps the best contemporary monograph on the subject.

ZONDEK, B: *Clinical and Experimental Investigations on the Genital Functions and their Hormonal Regulation* Williams & Wilkins Company, Publ, Baltimore (1941).

A small-format booklet (264 pages, 59 illustrations, 44 tables, 269 references), in which one of the masters of sex-hormone research summarizes his recent clinical and experimental investigations in this field The booklet makes highly-stimulating reading, especially for those personally engaged in *pertinent investigations,* but it does not attempt to cover the entire relevant literature.

A textbook chiefly concerned with the endocrinologic problems encountered in gynecologic practice (571 pages, 157 illustrations and numerous references) The principal emphasis is on the clinical problems, but a good deal of space is also devoted to the theoretic aspects of female endocrinology, the physiology and pathology of the endocrine organs not directly related to sex are likewise briefly surveyed The book is highly recommended, especially to gynecologists.

HOFFMAN, J *Female Endocrinology. Including Sections on the Male* W. B Saunders Company, Publ, Philadelphia (1944).

An extensive treatise (788 pages, 180 illustrations and numerous references) concerned mainly with the endocrinologic aspects of gynecology from the clinical point of view. However, a good deal of space is also devoted to the theoretic evaluation of the pertinent diseases The most important endocrine derangements of the testis are likewise reviewed An appendix deals with the principal bioassay and analytic methods for the determination of hormones Useful tables summarize the most important pharmaceutical products of sex hormone preparations

KURZROK R *The Endocrines in Obstetrics and Gynecology* The Williams & Wilkins Company, Publ, Baltimore (1937)

A book (488 pages, 178 illustrations numerous references) dealing with the application of endocrinology to gynecologic practice The physiology and pathology of those endocrine glands which are not directly concerned with gynecology is also briefly reviewed

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MORICARD, F *Hormonologie Sexuelle Humaine* Masson et Cie Paris (1943)

A monograph (377 pages, 101 illustrations and numerous references) concerned with the physiology and pathology of sex, as applied to clinical problems The volume contains many interesting observations and hypotheses, but is highly subjective in its interpretations (In French)

MORICARD, R.: *Facteurs Hormonaux et Cytoplasmiques de la Division Nucleaire. Meiose et Gonadotrophines* Masson et Cie, Paris, (1940).

A book (366 pages, numerous illustrations and references) describing the influence of hormonal factors upon nuclear division (especially miosis) and the formation of polar bodies in ova, as well as miosis in somatic cells. The treatise is mainly based upon the author's personal investigations in this field (In French)

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A *monograph (444 pages, 27 illustrations* and several hundred references) concerned with the various types of intersexuality in man A brief appendix deals with similar *lesions in animals. Main emphasis* is laid upon morphologic problems (In German)

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A symposium (223 pages, few illustrations but numerous references), in which the histology and pathogenesis of mammary tumors in mice, is discussed in detail. Special sections are devoted to the influence of hormones, the milk factor,' diet, etc. Each chapter is written by a competent investigator with personal experience in this field The book probably represents the best source of information concerning this subject

NOVAK, E *Textbook of Gynecology*: The *Williams & Wilkins Company* Publ, Baltimore (1944)

An excellent textbook (708 pages, 456 illustrations and a fair number of references) dealing with gynecology as a whole, but placing adequate attention upon the important rôle played by hormones

PEARLMAN, W H *Chemistry and Metabolism of Progesterone* In The Hormones Pincus, G and K V Thimann (Ed) Academic Press Inc Publ, New York (1948)

An excellent review (58 pages, numerous tables and charts, 233 references) compiled mainly from the chemist's point of view. Clinical implications are only touched upon

PEARLMAN, W H *The Chemistry and Metabolism of the Estrogens* In The Hormones. Pincus, G and K V Thimann (Ed), Academic Press Inc Publ, New York (1948)

An excellent review (54 pages, numerous tables and charts, 206 references), compiled

logic motives involved in this discovery, I should like to relate them in detail.

After the First World War, *Banting* — returning from military service — took up medical practice in the comparatively small town of London, in the Province of Ontario, in Canada. One evening, he read an article on the degenerative changes which take place in the pancreas after blockage of its duct by concrements. He went to bed, but could not sleep, due to the intriguing though vague impression that such degenerative changes might help the elucidation of the then mysterious part played by the pancreas in diabetes. It was not until about 2 o'clock in the morning that the idea suddenly crystallized in his mind, which he immediately jotted down on a piece of paper in the words: "Ligate pancreatic ducts of dogs. Wait six to eight weeks for degeneration. Remove the residue and extract."

Many investigators find it difficult to clearly formulate an idea in the presence of the many psychologic inhibitions which arise when one is fully awake; on the other hand in the half-conscious state, while about to fall asleep or to awaken, instinctively felt conceptions tend to present themselves clearly without any effort.

Banting could not carry out his plan in London, Ontario, hence he visited Professor *J. J. R. Macleod*, at the University of Toronto, Canada; from him, he received the advice and the facilities necessary to perform his experiments Work began on the 16th of May, 1921, with two young medical students, *Best and Noble*, who were appointed as *Banting's* assistants, to help him during one month, each in succession The boys tossed a coin to decide who should start and *Best* won. Since *Noble* did not return at the end of the month, *Best* continued to help *Banting* during the rest of the work and contributed many fertile thoughts to make this enterprise successful. He is the now well-known physiologist, *Prof. C. H. Best*, Banting's successor in the directorship of the Banting-Best Department of Medical Research, at the University of Toronto.

After several failures, on July 27th, 1921, *Banting* and *Best* finally had a duct-tied dog with a degenerated pancreatic residue and a severely diabetic, completely depancreatized dog. The degenerated pancreatic remnant of the first animal was removed, cut up in small pieces and extracted in the cold, with about 100 cc. of saline. 5 cc. of this extract was given intravenously to the depancreatized dog and 2 hours later, its blood sugar had fallen from 200 to 110 mg. per 100 cc. By January *1922*, the first diabetic patients were treated with cattle-pancreas extracts at a hospital in Toronto.

It is interesting to note that several earlier workers (*Hédon, Zuelzer, Rennie and Fraser, Scott*) obtained suggestive results with pancreatic extracts, but ascribed the hypoglycemic reactions to the "toxicity" of their preparations. In France, the well-known physiologist, *E. Gley*, had performed experiments, very similar to those of *Banting*, 16 years earlier (1905). He even described them in a private communication, which he deposited, in a sealed envelop, with the Societe de Biologie de Paris, in February, 1905. *Gley* injected oil into the pancreatic duct and thus caused the gland to sclerose (*Claude Bernard's* method.) He noted that such dogs do not become diabetic and that intravenous injection of extracts of these sclerosed glands diminish the glycosuria of pancreatectomized dogs. Only in 1922 after *Banting's* publication did Gley give permission to open this sealed letter, and subsequently, a great deal was written about the moral aspects of handling such a priority.

V

THE PANCREAS

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HISTORIC INTRODUCTION

The existence of the pancreas (from the Greek: pan=all and kreas=flesh) was known as an "abdominal salivary gland" to ancient physicians, but the endocrine cell accumulations, which are distributed throughout the organ between the exocrine glandular elements, were first observed by *Paul Langerhans*, in 1869. Later, *Laguesse* (1893) named them the "islets of Langerhans" or "Langerhans' islets" and ascribed an endocrine function to them, on purely hypothetic grounds.

Diabetes mellitus. — This disease was mentioned in the Egyptian Papyrus of Ebers (1500 B.C.) and was known to the ancient Greeks; indeed, it was they who gave the name diabetes (syphon) to this condition because of its most prominent manifestation, the polyuria. During the first century, *Aretaeus of Cappadocia* (30-90 A.D.) described the condition as a "melting down of the flesh and limbs into urine." *Thomas Willis* of Oxford (died 1675) is usually credited with the heroic discovery that the urine of diabetic patients has a taste "as if imbued with honey and sugar," although the sweetness of the urine had been previously mentioned by the Indian physician *Susruta* (500 A.D.). The actual presence of sugar in the urine was subsequently demonstrated by *Dobson* (1776). *Cullen* (1709-1790) added the adjective "mellitus" (melitoes = honeyed or sweet) to distinguish the disease from the "insipid" diabetes. *Chevreul* (1815) demonstrated that the sugar in question is identical with that found in grapes. It was only much later that acetone (*Petters*, 1857), acetoacetic acid (*Gerhardt*, 1874) and finally β-hydroxybutyric acid (*Kutz*, 1845-1895) were also demonstrated in the urine of diabetics.

The understanding of normal and abnormal sugar metabolism was greatly promoted by the classic investigations of *Claude Bernard* (1848), who discovered glycogen and found that the liver can store it as well as form blood sugar from it.

The important rôle of the pancreas was first demonstrated (in the same year in which Brown-Sequard reported his famous experiments) by *v Mering and Minkowski* (1889) who removed the gland and thus coincidentally produced experimental pancreatic diabetes in dogs.

Insulin. — *de Meyer* (1909) gave the name "insulin" to the — at the time still hypothetic — internal secretion of Langerhans' islets. It was undoubtedly the merit of *Banting and Best* (1921) however, to prepare the first pancreatic extract which consistently alleviated the manifestations of diabetes in pancreatectomized dogs. This was accomplished thanks to the elimination of the insulin-destroying enzymes of the pancreas, by causing compression atrophy of the acinar tissue through ligation of the ducts.

A number of interesting lessons can be learned from the history of insulin. Since I had the opportunity of personally discussing at some length, with *Sir Frederick G. Banting*, the psycho-

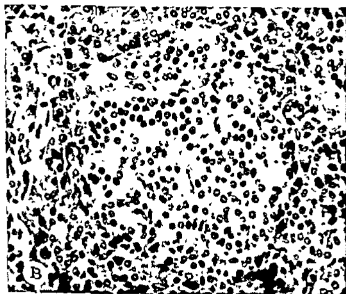
where the "*head*" of the pancreas adheres intimately to the middle portion of the duodenum. The head is somewhat thicker than the rest and its lower part contains a groove through which the mesenteric vessels pass (see: p. 90).

In the adult human being, the pancreas weighs 65-160 gm; it measures about 15-25 cm. in length and 2-8 cm. in thickness.

HISTOLOGY

The bulk of the pancreas consists of the EXOCRINE TISSUE with which we are not concerned here. Essentially, it is a compound, acinous gland whose digestive juice is eliminated into the duodenum, through a large main duct (of Wirsung) and a smaller accessory duct (of Santorini).





Normal Pancreas (Man). — A. Note light Langerhans islets in the midst of the darker acinar tissue. A few *larger ducts are also clearly* visible. — B. Higher magnification of a single Langerhans islet. The various endocrine cell types cannot be clearly distinguished on this photograph, but most of the beta-cells are in the periphery.
(Courtesy of Dr. W. Bonin.)

There are many similar instances in the medical literature. An important observation is made but the discoverer is somewhat uncertain about it or fails to realize its implications. Hence he makes only incidental reference to the chief point or even omits to mention it. In such cases, the "discoverer" deserves less credit than he, who not having been accidentally confronted with an important fact, had no opportunity to give such evident proof of his inaptitude to evaluate it. If a scientist makes no important observation he deserves no credit, but can blame "chance"; however, if a significant fact comes his way and he lacks the vision to see its importance, he can only blame himself The element of chance, in medical discoveries, is overrated in any case. Chance is a lady who smiles only upon those who know how to appreciate her artful charms; these connaisseurs she rarely neglects. — The secret of the game is art appreciation.

Collip devised the first improvements for the preparation of simple extracts. Later *J J Abel* (1927) succeeded in isolating insulin crystals and subsequently, *D A Scott* (1939) found that the crystalline insulins are salts of proteins with such metals as zinc, cobalt, cadmium or nickel

Hagedorn (1936) and his co-workers discovered that compounds of insulin with any one of several protamines (simple proteins) exert a slower and more prolonged anti-diabetic effect than ordinary ("regular") insulin, because combination with protamine delays the absorption of the hormone This and various other slowly acting "modified insulins" — especially protamine-zinc-insulin *(Scott and Fisher, 1936)* — make it possible to decrease the number of injections necessary to maintain sugar metabolism within normal limits.

Thanks to all these discoveries, experimental endocrinology made one of its greatest contributions to clinical medicine in the form of a simple therapy for diabetes.

Hypophyseal and Adrenal Diabetes. — The pancreas is not the only endocrine gland involved in the pathogenesis of diabetes. This was shown by animal experiments revealing that hypophysectomy (*Houssay and Biasotti, 1930*), or removal of the adrenal cortex (*Long and Lukens, 1936*), alleviates pancreatic diabetes. It was subsequently demonstrated that these glands (the hypophysis and the adrenal cortex) elaborate diabetogenic hormones. Indeed, *F. G. Young* (1937) found that anterior-hypophyseal extracts can produce degeneration of Langerhans islets, and permanent diabetes, in dogs.

Hyperinsulinism — The manifestations of insulin intoxication had already been noted by *Banting* and *Best* (1921), but it was *Harris* (1924) who first suggested that spontaneous overproduction of insulin by the pancreas may be the cause of a clinical syndrome in man Subsequently, *Wilder* et al (1927) published the first case of an islet-cell carcinoma whose hepatic metastases were shown to contain a large amount of insulin and *Howland* (1929) proved that surgical removal of an islet-cell adenoma could cure the condition of hyperinsulinism.

NORMAL MORPHOLOGY

ANATOMY

In man, the pancreas is a grayish-pink retroperitoneal organ situated at about the level of the second and third lumbar vertebrae Its left extremity, the "*tail,*" commences near the spleen, hence the "*body*" extends transversely across the abdomen towards the right,

and the endocrine cells originate from the embryonic ducts.

The islet cells develop in embryos of 3.5-4.5 cm. crown-rump length but specific granules appear in them only at about the 31 cm. stage.

THEORIES CONCERNING THE HISTOPHYSIOLOGY OF THE PANCREAS

It is a much debated question WHETHER, DURING POSTNATAL LIFE, ACINAR OR DUCT CELLS CAN TRANSFORM THEMSELVES INTO ISLET CELLS AND VICE VERSA. During embryonic life the formation of islets from ducts is certainly possible, yet, following partial pancreatectomy, after destruction of islets by pituitary extracts or by alloxan, no significant regeneration of islet tissue takes place through the transformation of acini into islets.

On the other hand, it is probable that ONE TYPE OF ISLET CELL MAY BE TRANSFORMED INTO ANOTHER, since numerous intermediate types are detectable between α- and β- cells. Even this transformation does not appear to proceed easily, however, since selective destruction of the beta cells (pituitary extract, alloxan) is rarely followed by any significant transformation of other cells into this type

The assumption that a considerable amount of INSULIN IS SECRETED INTO THE LYMPHATICS of the islets, has not been confirmed and it is now generally accepted that the hormone is discharged directly into the blood capillaries.

The following facts are of importance in connection with the histophysiology of insulin secretion :

The PANCREAS INFLUENCES CARBOHYDRATE METABOLISM THROUGH A HORMONE :

(1) Pancreatectomy causes diabetes
(2) Transplantation of a pancreas, by vascular anastomosis onto the neck of a pancreatectomized animal, prevents the development of diabetes.

The PANCREAS ACTS BY VIRTUE OF ITS ISLET TISSUE :

(1) The islets have no ducts and exhibit the histologic characteristics of an endocrine gland.
(2) In the teleosts, selective extirpation of the islet tissue is technically feasible and produces a diabetes curable by islet extracts.
(3) Insulin is present in pancreatic tissue whose exocrine elements underwent pressure atrophy following duct ligation, but whose Langerhans islets remain intact.
(4) Following extensive, partial pancreatectomy, diabetes develops gradually and in proportion to the progressive degeneration of the islets.
(5) Hyperinsulinism in man is produced by neoplasms whose parenchyme consists exclusively of islet cells and is cured by their surgical removal.
(6) Islet-cell adenomas, and even the metastases of islet-cell carcinomas, may be rich in insulin.

The β-CELLS ARE THE PRODUCERS OF INSULIN :

(1) The development of diabetes, following extensive partial pancreatectomy, is proportional to the progressive degeneration of the β-cells, in particular.
(2) Diabetogenic anterior-pituitary extracts exert a specific damaging effect upon the β-cells, and simultaneously decrease the insulin content of the pancreas in proportion to the β-cell degranulation produced.
(3) The β-granules, like insulin, are highly soluble in alcohol.
(4) High carbohydrate diets cause degranulation of the β-cells.

The ENDOCRINE TISSUE is distributed throughout the organ between the exocrine-glandular elements, *in the form* of small cell accumulations, the "Islets of Langerhans." Their number in the human pancreas varies between 200,000 and 1,800,000 and their diameter between 75 and 175μ. The total volume of the islets is about 1/100 of the whole pancreas. They are somewhat *more numerous in the tail than in the* body or head. These islets are extremely vascular and often reveal close connections with the smaller ducts, from which they are presumably derived.

The EPITHELIAL CELLS of the islets are essentially of four varieties: the *alpha, beta, gamma and delta cells.* The α-cells contain acidophilic, alcohol insoluble granules and are less numerous than the beta cells, whose granules are basophilic and alcohol soluble. The *β-cells generally occupy the periphery* of the islets and are smaller than the other varieties. Special staining technics have been devised which facilitate the recognition of the various cell *types by selective coloration* (Mallory-azan, Bensley stain). The γ-cells contain no granules *δ-cells have been* described in various species but are less clearly defined.

The STROMA of the islets is a particularly delicate connective tissue network *which carries the capillaries.* A thin reticular membrane may delimit the islets from the exocrine tissue but, in some places, the islet cells seem to be in direct contiguity with acinar or duct cells.

The ARTERIES of the pancreas come from branches of the celiac (through the superior pancreatico-duodenal and splenic) and the superior mesenteric (through the inferior pancreatico-duodenal) arteries. The pancreatic VEINS accompany the *arteries and* discharge the blood into the portal vein

The LYMPHATICS of the pancreas drain mainly into the celiac lymph *nodes.*

The pancreatic NERVES are predominantly unmyelinated branches of the celiac plexus, which accompany the arteries and terminate among the acini *and islets. There are also* some myelinated fibers from the vagus, whose non-myelinated endings appear to pierce the islets. It may be recalled in this connection that vagus stimulation *appears to cause insulin secretion and* that some workers claim to have traced the pertinent pathways to the hypothalamus. The pancreas also contains occasional sympathetic GANGLION CELLS *and, in certain places, the islet cells* appear to be intimately intermixed with nervous elements. These structures have been termed "NEURO-INSULAR COMPLEXES."

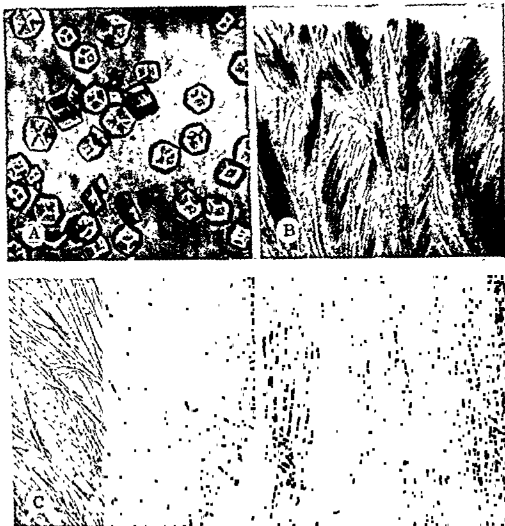
COMPARATIVE MORPHOLOGY

The pancreas *contains both* exocrine and endocrine elements in all vertebrates. It is of special endocrinologic interest that in certain teleost FISH, islet-tissue develops separately from *the exocrine elements of the* pancreas These islet-cell accumulations have been called the "Stannius *bodies.*"

In several species of BIRDS (fowl, duck, goose, pigeon), the entire pan*creas is situated* within a single loop of the duodenum, while in many RODENTS, pancreatic *tissue is rather* diffusely distributed throughout a large portion of the peritoneum, this *renders* pancreatectomy particularly difficult.

EMBRYOLOGY

The pancreas develops in 3-4 mm human *embryos from* two diverticuli, arising respectively from the dorsal and ventral wall of the *duodenum.* The dorsal pancreas forms the body, tail and part of the head; the *ventral* primordium contributes only a small portion of the organ. Both the exocrine



Various Insulin Crystals. — A. Zinc-Insulin — B. Piperidine-Insulin — C. Iso-Amylamine-Insulin. — D. N-Amylamine-Insulin. (Courtesy of Dr D A Scott)

of insulin nor the chemical prerequisites for its activity have as yet been elucidated Various proteases inactivate the hormone by digestion: glutathione, through its sulfhydryl groupings, may reduce the cystine disulfide-linkage in insulin and inactivate the hormone through this mechanism

GENERAL PHARMACOLOGY OF INSULIN

STANDARDIZATION

Chemical Methods. — There are no satisfactory chemical methods for the estimation of insulin

Bioassay. — The activity of insulin preparations is usually estimated by the lowering of the blood sugar in fasting RABBITS or the production of convulsions in fasting MICE. In either case, the effects obtained with the unknown preparation should be compared with those of a known standard. T' is referred to the Pharmac' United States (U.S P XIII,

This is presumably a sign of compensatory hormone secretion.

(5) Insulin causes degranulation and involution of the β-cells as well as a decrease in the insulin content of the pancreas. This is presumably as a result of compensatory atrophy.

(6) Alloxan is a drug which damages the β-cells in a rather specific manner. It causes a type of pancreatic diabetes whose severity parallels the β-cell damage produced.

CHEMISTRY OF THE PANCREAS

CHEMICAL COMPOSITION OF THE GLAND

Apart from its insulin content, chemically, the outstanding characteristic of the pancreas is the high PRO-ENZYME concentration. It contains the precursors of trypsin, chymotrypsin, carboxypolypeptidase, amylase, lipase, rennin, and maltase. These pro-enzymes are readily activated by contact with tissues, hence pancreatic substance or juice, accidentally spread over the peritoneal organs at the occasion of an operation, is particularly irritating. For the same reason, the insulin of the islets is destroyed if mixed with the remaining pancreatic tissue without taking special precautions.

CHEMISTRY OF INSULIN

In preparing insulin from pancreatic tissue, it is of especial importance to protect the hormone against digestion by the pancreatic ENZYMES. Insulin is relatively unstable in alkaline solution but pancreas may be incubated under aseptic conditions in neutral or acid media without destroying its insulin Pepsin-HCl and activated proteolytic, pancreatic enzymes destroy insulin. Trypsinogen has no effect upon insulin, however, and pancreas can be incubated with it at 37° C. for several hours without any loss of insulin. The hormone is usually extracted with the aid of acidified alcohol.

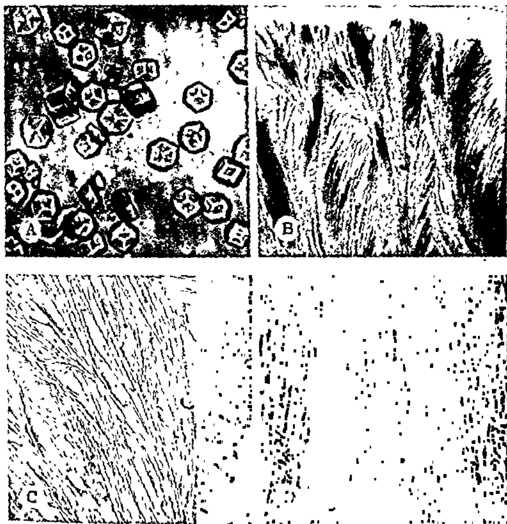
The molecular weight of insulin is about 46,000. It usually crystallizes in the form of twin rhombohedra of microscopic size, as long as certain METALS such as zinc, cobalt, cadmium or nickel are present in the solution. Zinc-insulin crystals contain 0.15-0.5% zinc but the metal does not occur in constant amounts. It is noteworthy in this connection that pancreatic tissue is particularly rich in zinc.

Zinc-insulin crystals prepared from the pancreas of diverse animals (human, dog, cattle, fish, bison, or sheep) have the same biologic potency: and the same immunologic, physical and chemical properties This protein hormone is therefore apparently not species-specific

Insulin is rich in cystine and as a result of this, has a SULPHUR content of as much as 3.2%. The entire insulin molecule appears to consist of amino-acids only. Their percentual distribution is still incompletely known, but analyses reveal ·

leucine	13.3
glutamic acid	21.0
cystine	12.0
tyrosine	12.0
proline	10.0
histidine	4 0
arginine	3 0
lysine	2.0
phenylalanine	8.4

In spite of persistent efforts to determine whether any one specific part in the insulin molecule is the ACTIVE GROUP responsible for its hormonal action, neither the complete structure



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the technical details and mathematical evaluation of such tests, which are too complex to be included here.

The INTERNATIONAL STANDARD is a crystalline zinc-insulin preparation defined as containing 22 units per mg.

PHARMACOLOGY OF SPECIAL INSULIN PREPARATIONS

REGULAR OR UNMODIFIED INSULIN is usually distributed as the water-soluble hydrochloride in a solution containing 20, 40 or 80 units per cc.

CRYSTALLINE INSULIN *is obtained by* the addition of small quantities of zinc acetate. It is prepared in aqueous solutions containing 40 to 80 units per cc. Like the former it is very readily absorbed and hence acts quite rapidly. An average dose depresses the blood sugar within 30 minutes, the effect reaching its peak after 3-4 hours and disappearing within 6-8 hours.

PROTAMINE-INSULINS are prepared by the formation of compounds between ordinary or unmodified insulin and one of the protamines The advantage of these protamine-insulins, is that they are more slowly absorbed and hence act longer and more uniformly than the rapidly absorbed, regular-insulin preparations. Thus, depancreatized dogs, even if they receive a liberal diet, may be maintained sugar-free with a single daily dose of protamine-insulin; it is rarely used in clinical medicine.

Further improvement, due to even greater delay in activity, is obtained by the addition of zinc to protamine insulin. A stable, opalescent suspension of PROTAMINE-ZINC-INSULIN, containing 40-80 units per cc., is one of the most popular preparations of the hormone. In clinical diabetes it is usually given only once daily Some specialists prefer a 2:1 or 3.1 mixture of regular and protamine *insulin*.

Other modified insulins are obtained by combination of the hormone with HISTONE, GLOBIN, etc.

In order to decrease the possibility of errors, ampules of U.S.P. insulin preparations are *marked with labels whose* color is indicative of their hormone-concentration (see : N.N.R.)

MODE OF ADMINISTRATION

As other protein hormones, insulin is inactive when given by the ORAL ROUTE. In spite of extensive investigations, no adequate orally-active insulin preparation is as yet available.

Usually, the hormone is given SUBCUTANEOUSLY, *less often* INTRAMUSCULARLY, the INTRAVENOUS route being reserved for emergencies such as diabetic coma. (For dosage, see: pages 529-531.)

SENSITIZATION AND DESENSITIZATION

Although allergic sensitivity can develop to the proteins of certain insulin preparations, there is no clear-cut *evidence of any unusual, acquired sensitivity* of the hormonal effect as a result of pretreatment.

In addition to the not uncommon occurrence of primarily insulin-resistant diabetic patients, it has occasionally been reported that an originally insulin-sensitive individual became resistant to the hormone in the course of prolonged therapy. There is no definite proof to indicate, however, that *in these instances resistance was acquired* as a result of insulin treatment, due to some specific defense reaction or antihormone formation.

THEORIES CONCERNING INSULIN

Biogenesis. — The histophysiology of insulin formation has been discussed in a previous chapter but definite information is not yet available, concerning the chemical mechanism of its biogenesis

Fate of Insulin in the Body. — Parenterally injected insulin does not appear to be selectively destroyed by

the liver as so many other hormones (e.g., steroids) are. It is noteworthy, in this connection, *that insulin is the only hormone which normally passes through the liver before reaching the general circulation.* Nature has perhaps provided this arrangement to supply *the hepatic tissue — one of the main target organs upon which insulin acts* — with the greatest concentration of the hormone.

Even following administration of large doses of insulin, no significant amounts are demonstrable in the urine and the concentration in the blood declines very rapidly after intravenous *injection of the hormone*. Presumably the blood proteases destroy insulin soon after it enters into the circulation.

Mechanism of Insulin Action. — Although the mechanism through which insulin exerts its physiologic effects is still incompletely known, the following facts appear to be well established

INSULIN DECREASES GLUCONEOGENESIS AND GLYCOGENOLYSIS *in the liver* of pancreatectomized animals. In fact, it has been claimed *(Soskin et al.)* that the principal action of insulin is to *lower the level at which the blood* sugar is homeostatically held by the liver, and that it does so by inhibiting the hepatic glucose output. Simultaneous blood sugar (and blood flow) determinations on the afferent and efferent blood vessels of the liver furnished the most important evidence in favor of this interpretation (see p. 492).

INSULIN FACILITATES GLUCOSE UTILIZATION, as judged by the fact that both in the normal and in the diabetic individual, it permits efficient carbohydrate *utilization at comparatively low* blood sugar levels.

In the diabetic, insulin raises the R.Q. This has been considered indicative of increased carbohydrate utilization. However, in the normal individual, insulin causes only slight and inconsistent variations in the R.Q.

Insulin increases the rate of GLYCOGEN DEPOSITION in the muscles and liver of *depancreatized animals.* Glycogen may also be deposited in the liver, and especially, in the muscles of pancreatectomized dogs which are not treated with insulin: but under the influence of this hormone, glycogen deposition is *considerably accelerated. Administration* of extra insulin to normal animals may decrease the liver glycogen. The reasons for this paradoxic effect are not clear. (Adrenaline liberation?)

As judged by the evidence mentioned above, some of the most important actions of insulin are mediated through the liver: yet, insulin is also EFFECTIVE AFTER HEPATECTOMY, inasmuch as it *enhances the deposition of muscle glycogen and the oxidation of sugar.*

Even in perfused limb preparations, insulin augments the formation of glycogen from the glucose of the perfusion fluid, and *indeed, the hormone stimulates the respiration of pigeon breast*-muscle or baker's yeast in vitro. The interpretation of these data is difficult, however, since insulin does not cause a *lowering of sugar concentration when* directly added to blood in vitro, nor does it exert any direct effect upon the sugar consumption of most other in vitro tissue preparations.

All these observations clearly indicate that the most important mechanisms through which insulin influences carbohydrate metabolism are

(1) Decreased rate of sugar formation from noncarbohydrate sources (gluconeogenesis).
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THEORIES OF DIABETES

NON-UTILIZATION (Minkowski)		OVERPRODUCTION (v Noorden and Isaac)	
Pro	Con	Pro	Con
Arteriovenous blood sugar difference low in systemic circulation of diabetic	Even normally arteriovenous blood sugar difference is often extremely slight, and in any case, this is not significant without blood-flow determinations	Arteriovenous blood sugar difference in liver is increased after pancreatectomy, even at comparable blood-flows	There are no convincing arguments against the overproduction theory. The few investigators who disbelieve this concept do so because they consider the arguments in favor of the non-utilization theory to be conclusive. — This reasoning is faulty since the two theories are not mutually exclusive Apparently there is always overproduction and, at least at low blood-sugar levels, also diminished utilization
Exogenous glucose is quantitatively excreted in severe diabetes	Excretion of exogenous glucose would be approximately quantitative, if glycemia is above renal threshold, irrespective of whether diabetes is due to non-utilization or overproduction	Peripheral tissues of pancreatectomized animals use just as much sugar at "diabetic" blood sugar levels as do those of normal animals at normal glycemic levels. The additional large quantities of glucose lost in the urine after pancreatectomy must be due to overproduction Most investigators who support the overproduction theory do so by elimination, since they believe that the arguments against the non-utilization theory are conclusive.	
The low R Q of fasting (0 7) does not rise after carbohydrate administration in diabetes	R Q does not rise after carbohydrate administration, since sugar is quantitatively eliminated, due to superabundance		
Insulin raises the R Q in diabetes	Low R Q in itself is insignificant, since it may be due to intermediate metabolic reactions		
Less glucose must be infused per hour in hepatectomized and pancreatectomized, than in only hepatectomized dogs to maintain normal glycemia	After hepatectomy, endogenous blood sugar disappears just as rapidly in pancreatectomized as in normal animals		
The development of diabetic ketosis due to decreased ketone utilization (This could not occur while carbohydrate is adequately burned)	Diabetic tissues actually consume normal amounts of ketone bodies	Ketone body production by the liver is demonstrably increased in diabetes Hence ketosis due to overproduction.	
Urine D N ratio is so constant (2 8 1) that apparently, all glucose is excreted	Constancy of D N ratio has not been confirmed by modern investigators		

sugar and ketone bodies. Since there is still no unanimity of opinion concerning this point, we merely tabulate the principal relevant arguments. It must be kept in mind, however, that the two theories are not mutually exclusive, since insulin could affect both the utilization and the production of carbohydrates.

Very little is known about the immediate, PRIMARY CHEMICAL MECHANISM through which insulin exerts its action. It is highly probable, however, that it affects the activity of enzymes (hexokinase) regulating intermediate carbohydrate metabolism. (For pertinent data see: pp. 494, 495.) In any case, most of the manifestations of insulin overdosage (e g , nervous and gastrointestinal disturbances, sweating, compensatory adrenaline discharge) are secondary to its effect upon carbohydrate metabolism, since they are completely prevented by glucose administration.

(For the relative participation of pancreas and liver in regulation of blood sugar level, see also the discussion on pp. 491-496.)

Different Kinds of Pancreatic Hormones. — It has been claimed that the pancreas produces a number of hormonal substances, in addition to insulin, for instance VAGOTONIN (a blood-sugar-depressing substance different from insulin), GLUCAGON (a blood-sugar-raising principle), KALLIKREIN (a blood-pressure-depressing principle of the pancreas which is eliminated in the urine), etc. None of these substances have been proven to be true hormones.

LIPOCAIC is the name given (by *Dragstedt*) to the substance present in crude pancreas, which is responsible for the prevention of fatty-liver formation when the gland tissue is fed to pancreatectomized animals. The chemical nature of lipocaic is still unknown and it appears that a number of substances can prevent fatty-liver formation (see p. 496).

In conclusion, we may say that there is no definite proof that the pancreas produces any hormonal substance other than insulin.

EXPERIMENTAL PHYSIOLOGY OF THE PANCREAS

EXPLANTATION OF THE PANCREAS

Because of the toxic properties of its enzymes it is extremely difficult to explant pancreatic tissue. The fact that islet tissue can grow in vitro has been clearly demonstrated however, with material obtained from human islet-cell adenomas.

TRANSPLANTATION OF THE PANCREAS

Since the enzymes of the pancreas prevent successful transplantation of slices of pancreatic tissue, permanent pancreatic grafts can only be obtained if the excretory tissue of the gland has been destroyed by duct ligation. It is noteworthy, however, that important information concerning the physiology of the pancreas has been obtained by the vascular anastomosis technic. The customary procedure is to unite, in the dog, the artery of the pancreas with the carotid and its vein with the jugular. Thus one or even several pancreases may be temporarily grafted onto the neck of normal or pancreatectomized animals. Although the life-span of these grafts is not very long, they continue to form insulin and are useful in the study of the humoral factors which regulate insulin formation in the absence of nervous connections with the host's body.

TECHNIC OF PANCREATECTOMY

The DOG and CAT are most commonly used for the study of experimental pancreatic diabetes. In them, the pancreas

can be removed without difficulty if the organ is carefully separated (by blunt dissection) from the splenic and duodenal blood vessels as well as from the duodenum itself Care must be taken not to damage the intestine by rough handling and not to lesion the pancreatico-duodenal vein which courses through the gland.

In most other animal species, including man, the technic of pancreatectomy is essentially the same, yet a few special cases are noteworthy. We have mentioned already that in the TELEOST FISH, the principal islets are anatomically distinct and may be removed without extirpating the exocrine tissue. In BIRDS, the pancreas is often located in a narrow loop of the duodenum and can be readily removed by complete resection of that loop with subsequent end-to-end anastomosis of the cut ends. In RODENTS, in which the pancreas is very diffuse, it is customary to remove only about 95% of the gland. This is technically simple and satisfactory for most purposes, since the remainder gradually degenerates so that diabetes ensues after a 2-3 months latency period

A progressive chronic type of diabetes can be produced in the dog by the removal of about 9/10 of the pancreatic tissue. Especially on high carbohydrate diets, the islets in the pancreatic residue degenerate and the so-called "SANDMEYER DIABETES" results. (See p 501.)

Certain drugs such as ALLOXAN, which destroy the β-cells of the islets, can likewise be used for the production of experimental diabetes. (See p 505)

EFFECT OF PANCREATECTOMY AND INSULIN TREATMENT

State. — It is interesting, that following PANCREATECTOMY, carnivorous animals (e g., cat, dog) develop a very severe and rapidly fatal diabetes, while herbivora (e.g., duck, monkey, goat) and certain omnivora (e.g., swine) are resistant to the loss of the pancreas, especially because they are less subject to acidosis.

The most characteristic symptoms of pancreatic diabetes are persistent hyperglycemia, glycosuria, loss of weight in spite of polyphagia, polyuria, ketonemic acidosis, and great susceptibility to infections.

Overdosage with INSULIN (either in the pancreatectomized or in the normal individual) on the other hand, causes neuromuscular incoordination with eventual generalized convulsions due to hypoglycemia. All these effects may be prevented by adequate carbohydrate administration. Indeed, there are only very few changes (e.g., abnormal glycogen deposition in the liver), which insulin can produce if adequate amounts of sugar are provided. This indicates that almost all of the so-called characteristic effects of insulin intoxication are actually merely the results of hypoglycemia.

Temperature. — The body temperature tends to be subnormal, both in severe pancreatic diabetes (especially in coma) and in grave insulin overdosage. This is probably due to a failure of temperature regulation caused by the profound metabolic derangements of animals suffering from a serious insulin insufficiency or excess.

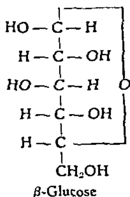
Basal Metabolism. — The B M R is usually not significantly altered, either by pancreatectomy or by insulin overdosage, but pancreatectomy decreases the respiratory quotient (R Q.) to about 0.7, probably as a result of decreased sugar utilization, increased gluconeogenesis or both Unlike in the intact individual, carbohydrate administration does not raise the R Q Insulin raises it, especially in the pancreatectomized animal and if carbohydrate is simultaneously given.

It will be recalled that the R Q is the ratio: $\frac{\text{Volume } CO_2 \text{ expired}}{\text{Volume } O_2 \text{ inspired}}$

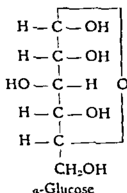
Since glucose contains enough oxygen to form one molecule of CO_2 for each molecule of O_2 absorbed, the R.Q. of glucose equals 1.0. The theoretic R.Q. of fat, on the other hand, equals 0.71. On an ordinary mixed diet the R.Q. is about 0.85.

Carbohydrate Metabolism. — Undoubtedly the most important metabolic function of the pancreas is its effect upon carbohydrate metabolism. In order to evaluate this profitably it will be useful to recall a few basic facts concerning carbohydrate metabolism in general.

The normal BLOOD GLUCOSE (dextrose) of man is an equilibrium mixture of two isomers, α- and β-glucose, both of which are dextro-rotatory, though not to an equal degree.



β-Glucose

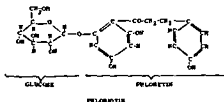


α-Glucose

With the usual analytic methods, the blood glucose concentration following a brief fast (to avoid postprandial hyperglycemia) is between 80 and 90 mg./100 cc. Most of the commonly used technics are based on the reducing properties of sugars, but since glucose is not the only reducing substance in the blood it must be remembered that part of the material determined as "glucose" is not sugar.

Only the liver participates appreciably in the *formation of blood glucose*, although perhaps the kidney also contributes traces. After hepatectomy, fatal hypoglycemia develops (whether the pancreas is present or not) because, with the liver, the main source of endogenous glucose is eliminated.

The liver can make blood glucose from its glycogen stores, simply by phosphorolysis, but it can also form glucose from non-sugar sources, such as protein (and perhaps even fat) through a process known as "*gluconeogenesis*." Some of the amino-acids (glycine, alanine, cystine, aspartic and glutamic acids) appear to produce glucose in theoretic amounts as shown by experiments on *phloridzinized animals*. *Phloridzin* (a glucoside from the root bark of apple, pear, plum or cherry trees), lowers the renal threshold for glucose so that a great deal of the glucose formed in the body is eliminated in the urine, from which it can be quantitatively recovered.

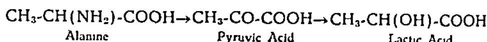


PHLORIDZIN

Tracer experiments with glycine suggest, however, that the sugar recovered from the urine, after administration of an amino-acid, is not necessarily derived from this acid directly.

The mechanism of this gluconeogenesis is not fully understood. To give

but one example, a possible pathway of glucose formation from the amino-acid alanine would be through the intermediary of lactic acid by oxidative deamination and subsequent *reduction* of the resulting keto-acid :



$$CH_3\text{-}CH(NH_2)\text{-}COOH \rightarrow CH_3\text{-}CO\text{-}COOH \rightarrow CH_3\text{-}CH(OH)\text{-}COOH$$

Alanine Pyruvic Acid Lactic Acid

Insulin inhibits gluconeogenesis while pancreatectomy augments it. Thus even fasting pancreatectomized animals continue to excrete large quantities of glucose This must come from non-sugars (probably body protein), since no great amounts of carbohydrates are stored (especially in the pancreatectomized animal) and no exogenous carbohydrate is available during fasting. If pure protein is fed to the pancreatectomized animal, most of it reappears in the urine as glucose. Insulin prevents this excessive gluconeogenesis in the above-mentioned test animals.

The *utilization of blood glucose* is not abolished in the absence of the liver, since intravenous glucose infusion raises the R.Q. and improves the general condition of the hepatectomized animal. It is also noteworthy that only *slightly* less glucose is required to maintain a normal blood sugar level in the pancreatectomized and hepatectomized *than in the merely hepatectomized animal. Insulin nevertheless improves sugar* utilization, as evidenced by the rise in R.Q. and the increased glucose tolerance it causes after pancreatectomy.

If two doses of glucose are given in *rapid succession, the second dose causes* a less pronounced hyperglycemia in normal individuals. Indeed, after the initial blood sugar rise, it may occasion an apparently paradoxic hypoglycemia. This so-called *Staub-Traugott* phenomenon has generally been ascribed to an excessive compensatory insulin secretion by the pancreas after it had been "alerted" by the first dose of sugar. As we shall see, however, blood sugar regulation by the liver is the most important cause of this phenomenon.

Comparative determinations of the amount of glucose entering and leaving the liver show that the *hepatic cell regulates the blood sugar* level through a stabilizing "homeostatic" mechanism. Thus, administration of glucose decreases, while hypoglycemia increases, glucose discharge into the venous blood of the liver. This blood sugar regulation is independent of any compensatory change in insulin secretion. It has been demonstrated even in completely pancreatectomized dogs whose blood sugar was maintained by a constant infusion of (exogenous) insulin, which obviously could not be influenced by glucose administration.

Following complete pancreatectomy, the administration of glucose causes a much more pronounced and more prolonged "diabetic type" of hyperglycemia; the Staub-Traugott effect also disappears. This observation was mainly responsible for the view that a *compensatory increase in insulin secretion is responsible for the phenomenon.* We know now, however, that this Staub-Traugott effect has another explanation In the pancreatectomized animal, whose glycemia is maintained at an approxi*mately* normal level with insulin, the Staub-Traugott phenomenon is positive In the intact organism, thanks to the endocrine activity of the islet cells, the homeostatic mechanism of blood sugar regulation is set for the normal blood sugar range. In the absence of the pancreas, the blood sugar regulating mechanism is, as it were, set at an almost infinitely high blood sugar level and hence, the administration of glucose causes no significant *compensatory* decrease in hepatic sugar production

Conversely, an excess of insulin sets the blood sugar regulating mechanism of the liver at an almost infinitely low level; this also precludes any effective regulation of the glycemia. Hepatectomized animals, whose pancreas is intact, likewise fail to exhibit the Staub-Traugott effect and they give diabetic blood sugar tolerance curves, probably because their hepatic blood sugar regulation is eliminated.

It appears that the participation of the liver, in the Staub-Traugott effect, is under the regulating influence of the anterior-pituitary since hypophysectomy likewise abolishes this phenomenon.

The interrelations between the pancreas and liver in the control of the blood sugar level have been compared with the factors which control the temperature in a thermostat furnace (Soskin). The heat in the furnace may be compared with the blood sugar, the thermoregulator mechanism with the liver, and the operator, who sets the level of the thermostat, with the pancreas and the other counter-balancing endocrine factors Insulin (the operator) sets the blood sugar level (temperature level) at which the liver (thermoregulator) is to maintain the blood sugar (heat in the oven), in spite of variations in exogenous and endogenous carbohydrate intake (variations in the temperature of the surroundings and in the heat-production of the oven). Obviously, if insulin lack or excess sets blood sugar regulation at a level outside of the effective range of the hepatic control mechanism, active blood sugar regulation becomes impossible. If a thermostat were set at a temperature above or below the effective range of its thermoregulator, heat regulation would likewise become impossible.

A variety of *agents are known to influence the hypoglycemic action of insulin.* Thus, numerous infections and intoxications inhibit the effect of the hormone, perhaps through the intermediary of the general-adaptation-syndrome which they elicit. Certain pituitary extracts, gluco-corticoids, as well as adrenaline inhibit the hypoglycemic action of insulin and all these hormones are secreted in excess during the general-adaptation-syndrome (see section on General-Adaptation-Syndrome).

Since the action of insulin upon blood sugar is chiefly mediated through the liver, all factors influencing the hepatic cells (e.g., hepatitis, fatty infiltration of the liver, hepatic cirrhosis), are likely to modify the effect of the hormone. It is known, furthermore, that alkalosis sensitizes, while acidosis desensitizes to the hypoglycemic action of insulin.

Anesthetics often inhibit insulin hypoglycemia, perhaps because they tend to cause asphyxia with secondary acidosis and to liberate adrenaline, factors which interfere with the actions of the hormone. (Chloralose and amytal are least effective in this respect.)

Various sugars alleviate the symptoms of insulin hypoglycemia in the presence of the liver, but, after hepatectomy only glucose is effective Upon intravenous injection, glucose is most efficacious, even in the intact organism, but mannose and fructose are also highly effective, while galactose, maltose, glycogen and glycerol have only a slight and transient effect. Sucrose, lactose and the pentoses are ineffective Of course, all carbohydrates capable of forming glucose are effective when administered by mouth. Some investigators believe that only glucose is directly oxidized in certain important tissues (e.g., central nervous system) and that hence, the efficacy of other intravenously administered carbohydrates depends entirely upon their conversion into *d*-glucose.

The ABSORPTION OF CARBOHYDRATES proceeds most actively in the small intestine; only traces are absorbed from the stomach or the large intestine.

Complex carbohydrates such as starches, dextrins, etc., are first broken down into monosaccharides by the intestinal juices. The resulting simple sugars can be absorbed even against a concentration gradient, that is, even if the blood sugar level is higher than the sugar concentration in the intestinal contents. During the absorption of such sugars as glucose and fructose there is an increase in the amount of esterified phosphate in the intestinal mucosa and it has been suggested that phosphorylation of sugars is a prerequisite for their absorption.

A variety of ingested monosaccharides, and indeed even non-sugars, can contribute glucose to the blood after first having been transformed into liver glycogen. There is reason to believe, however, that in the hepatectomized animal, glucose itself is most effective in satisfying the carbohydrate needs of the body. As with the alleviation of insulin hypoglycemia, other monosaccharides appear to raise the blood sugar, at least primarily because they are normally transformed into glucose by the liver.

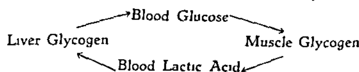
Following absorption of large quantities of glucose, some is oxidized and the remainder deposited as liver or muscle glycogen.

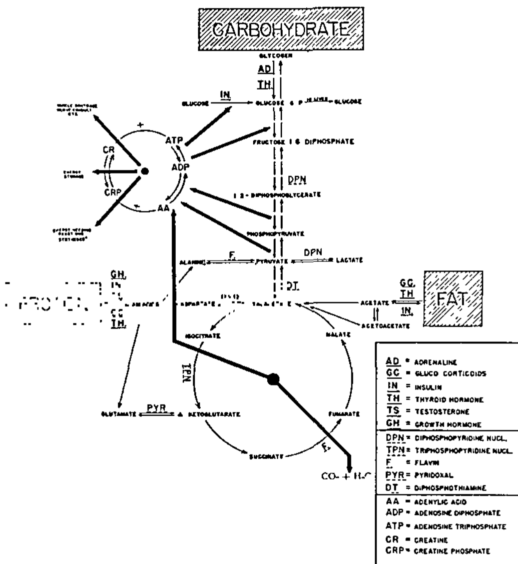
The breakdown and synthesis of glycogen in liver and muscles, as well as the combustion of glucose in tissues, are complicated processes which depend upon the action of various enzyme systems, the availability of oxygen, the presence of partially degraded carbohydrate metabolites suitable for resynthesis, etc It is not within the scope of this book to discuss all these factors in detail, but the diagram on p. 495 will help to remember the salient facts and act as a summary of the INTERMEDIATE METABOLISM OF CARBOHYDRATES.

It will be noted that the first stage in the utilization of glucose by the tissues is catalyzed by the enzyme *hexokinase*, namely the steps: glucose + adenosinetriphosphate → glucose-6-phosphate + adenosinediphosphate *This same step is also necessary for the transformation of glucose to glycogen.* It has been claimed that this reaction can be inhibited (both in vivo and in vitro) by anterior-pituitary extracts. Insulin counteracts this inhibition of the hexokinase reaction by the pituitary extract (in vivo and in vitro). This appears to be an important clue to the understanding of insulin action, especially since rats rendered diabetic by alloxan, yield tissue extracts which exhibit the same inhibition of hexokinase activity as is produced by anterior-pituitary extracts and here again, insulin removes the inhibition. Brain extracts represent an apparent exception since (in vivo), neither alloxan nor anterior pituitary extract inhibits hexokinase activity in them (Cori *et al.*, 1945).

It should be emphasized, however, that insulin is extremely effective in hypophysectomized animals, so that it would not be permissible to regard all insulin actions as due to removal of pituitary inhibition of hexokinase activity. (Cf p. 235.)

It must also be recalled, in connection with the hormonal control of intermediate carbohydrate metabolism, that a cycle exists in which liver glycogen forms blood glucose, this can be resynthesized into glycogen in muscles, the muscle glycogen is broken down to lactic acid and, while part of the latter may be resynthesized into muscle glycogen, another part is reconverted to liver glycogen. This is known as the lactic acid cycle or "Cori" cycle.





Schematic representation of the salient facts concerning the hormonal control of organic intermediate metabolism
(Constructed in collaboration with Dr R Levine).

their immediate degradation products and vice-versa

The Cori cycle is apparently most important during muscular exercise under conditions of comparative anoxia.

The conversion of glycogen to lactic acid in muscle extracts is not inhibited by anterior-pituitary extracts.

The STORAGE OF CARBOHYDRATES occurs almost exclusively as glycogen in the liver and muscles. Among other structures, only the decidua and the placenta are known to store significant amounts of carbohydrates. The muscle

glycogen is formed from blood glucose, while the liver glycogen can be synthesized either from lactic acid or from glucose or even from non-sugars by the above-mentioned process of gluconeogenesis

Pancreatectomy decreases the glycogen content of the liver but has a much lesser effect upon muscle glycogen and actually raises the glycogen content of the heart. This latter effect has generally been ascribed to glycogen formation from sugar, under the increased "head pressure" of the high blood sugar.

In the intact animal, insulin causes a considerable deposition of glycogen in muscles, without any very definite change in the liver. The glycogen deposition, which can be produced by insulin in the liver of the young rat, is probably due to minute amounts of adrenaline secreted in response to the insulin treatment Insulin also has a tendency to decrease the glycogen concentration of the liver in normal animals, probably because it increases adrenaline secretion, sugar consumption and muscle glycogen deposition.

On the other hand, in the pancreatectomized animal, insulin replenishes the depleted glycogen stores both in the liver and in the muscles, especially if the hormone is given in combination with glucose.

Renal ELIMINATION OF GLUCOSE OCCURS only if the blood glucose concentration exceeds the threshold level of 180 mg %, or if the renal threshold is artificially lowered, as in phloridzin intoxication or spontaneous renal diabetes

Only minute traces of glucose are present in normal urine, irrespective of the diet taken. True alimentary glycosuria is always indicative of some metabolic disturbance, since normally, any amount of glucose absorbed from the intestine is deposited and utilized at a rate which precludes a hyperglycemia in excess of the renal threshold (180 mg.%).

Lipid Metabolism. — Pancreatectomy causes a pronounced *derangement in lipid metabolism*, as evidenced by a marked, though transitory *hyperlipemia* (sometimes followed by hypolipemia), *hypercholesterolemia* and *fat deposition in the liver*. Adequate insulin treatment counteracts all these phenomena, without completely inhibiting, however, the fat deposition in the liver.

There is some evidence that part of the lipid metabolism disturbance is due to the lack of the external secretion of the pancreas. Even mere ligature of the pancreatic ducts causes disturbances in fat absorption due to the absence of pancreatic lipase in the intestinal tract. Conversely, feeding of pancreatic juice, raw pancreas or "lipocaic," prevents the abnormal fat deposition in the livers of depancreatized animals. A number of so-called *"lipotropic" substances* (choline, betaine, casein, methionine, inositol), share with the raw pancreas, the ability to prevent fat deposition in the liver following pancreatectomy, and it is rather probable that the activity of "lipocaic" is, at least partly, due to a mixture of several lipotropic factors of this type, rather than to a new hormone.

The mechanism through which insulin counteracts the hyperlipemia and hypercholesterolemia of the pancreatectomized animal is not fully understood It is debatable whether we should assume (as some authors do), that insulin acts on lipid metabolism by suppressing gluconeogenesis from fatty acids Yet this possibility may be considered, since, in the presence of fructose, fumarate or lactate, insulin inhibits the formation of ketone bodies in liver slices of diabetic cats In any event, it is highly probable that part of the action of insulin is due to the fact that it improves the utilization of glucose, and hence, diminishes the necessity of metabolizing fats.

The fact that pancreatectomized animals and severely diabetic patients usually lose their fat reserves likewise indicates that, in the absence of insulin, the fat stores are utilized to supply caloric energy.

In the normal individual, insulin has comparatively little effect upon lipid metabolism, although by increasing the appetite, it helps to form fat deposits. *It has been used for this purpose in the therapy of excessive leanness.*

ACETONE BODIES may presumably be formed either from fatty acids or from amino-acids but, in conformity with common usage, they will be discussed here in connection with lipid metabolism.

The physiologically important acetone bodies are:

Acetone: CH_3-CO-CH_3

Acetoacetic: CH_3-CO-CH_2-COOH

β-hydroxybutyric acid:
CH_3-CH(OH)-CH_2-COOH

Following pancreatectomy, the formation of acetone bodies from fatty acids and amino-acids is increased; consequently, excessive amounts of acetone bodies appear in the blood and urine. Acetone is apparently not produced as such, but merely represents a spontaneous decomposition product of acetoacetic acid.

Apparently, the acetone bodies are formed exclusively in the liver and only if the latter is under the influence of corticoid hormones. Thus, complete hepatectomy causes disappearance of acetone bodies in pancreatectomized animals. For efficient ketone production the liver must be under the influence of corticoids, hence adrenalectomy cures diabetic ketonuria, while corticoids restore it, however, changes in the renal ketone threshold also play a rôle here.

The diabetic organism can apparently utilize ketone bodies with the production of CO_2 and H_2O, to the same extent as the normal. In diabetes, as in many other conditions of insufficient carbohydrate utilization, ketosis occurs because of *an increased fat and protein* utilization. The old saying that "ketone bodies are burned in the flame of carbohydrates" is incorrect. It is true that ketosis rarely occurs in the presence of active carbohydrate combustion, but it is now generally agreed *that there is no direct relationship between* carbohydrate and ketone body combustion. In other words, the carbohydrates are anti-ketogenic rather than ketolytic. In the event of adequate carbohydrate utilization, less energy is derived from protein and fatty acids, *that is, from* ketogenic materials.

It is generally assumed that acetoacetic acid is the first ketone body formed; it is subsequently reduced to β-hydroxybutyric acid and finally transformed into acetone by *spontaneous decomposition.*

Nitrogen Metabolism. — The increased protein catabolism, occasioned by pancreatectomy, leads to a *rise in* the urinary elimination of *nitrogen;* this is counteracted by insulin therapy. It has been claimed that insulin increases the utilization of amino-acids by the muscles and stimulates *protein* synthesis. These *actions may be responsible for the decrease in the amino*-acid, creatine, creatinine and urea content of the blood caused by *the hormone, both in the intact and in the* pancreatectomized animal. Of course, some of the changes in protein metabolism are secondary to the *depression* of hepatic gluconeogenesis and the discharge of adrenaline occasioned by insulin. Adrenaline is known to decrease the amino-acid concentration of *the blood and insulin exerts this effect* only in the presence of the adrenals.

Salt and Water Metabolism. — The pronounced polyuria of pancreatectomized animals is mainly due to the fact that a large volume of urine is re-

quired to excrete the excessive quantities of glucose.

The changes in the electrolyte metabolism of the pancreatectomized animal are also primarily to be viewed as consequences of the deranged carbohydrate metabolism. Insulin hypoglycemia is accompaned by a simultaneous fall in blood potassium (K bound to hexosephosphate and glycogen) and inorganic blood phosphates (phosphate bound to hexosephosphate). It has been claimed that concurrently, the hexosephosphate content of the muscles and the adenosine-triphosphate concentration in the liver are likewise increased by the anti-diabetic hormone. There is some evidence that at least partly, these actions may also be due to secondary adrenaline liberation

Growth and Bone Structure. — Somatic growth is greatly inhibited by pancreatectomy, perhaps because ossification at the junction cartilages is deficient. These lesions are not completely corrected by insulin treatment unless it is complemented by simultaneous ingestion of raw pancreas. Interference with fat absorption, due to the abolition of the external secretion of the pancreas, causes the precipitation in the intestine of comparatively insoluble calcium soaps and hence, results in a secondary calcium deficiency There is also some derangement in the absorption of the lipid-soluble vitamin D, which is so important for ossification

Cardiovascular System. — Pancreatectomy does not tend to cause any serious cardiovascular damage in animals, although the occasional trophic disturbances are reminiscent of the diabetic gangrene which is so common in clinical diabetes

Nervous System. — The effect of the pancreas upon the nervous system is also of importance. Excessive POLYPHAGIA, following pancreatectomy, occurs in compensation for the increased catabolism. Insulin overdosage likewise causes a feeling of hunger, probably as a result of the hypoglycemia. Advantage has been taken of this effect in clinical medicine to augment the appetite of undernourished patients.

The hypoglycemic CONVULSIONS caused by insulin overdosage are presumably of nervous origin and mainly due to starvation of the nervous tissue, which is almost entirely dependent upon glucose as a fuel. Carbohydrates prevent this action of the hormone, yet there is no close correlation between the degree of insulin-hypoglycemia and the convulsions The reason for this lack of correlation is not known.

Convulsive doses of insulin are frequently used in the treatment of schizophrenia and other types of PSYCHOSES. In spite of extensive studies, the mechanism of this action has not been elucidated as yet, but the treatment is manifestly effective in suitably selected cases

The diabetic COMA and the concomitant disturbances in the function of the respiratory and thermoregulatory centers are due to the acidosis, and perhaps also to other toxic effects of accumulating acetone bodies They can be treated by combined administration of insulin and glucose

Heavy overdosage with insulin may lead to multiple small HEMORRHAGES IN THE CENTRAL NERVOUS SYSTEM but these are, at least partly, due to traumas incurred during hypoglycemic convulsions

Digestive System. — Insulin hypoglycemia is usually accompanied by increased tonus and motility of the stomach. Tetanic contractions of the stomach may thus be produced and generally persist until the hypoglycemia is relieved by sugar administration Bilateral vagotomy prevents this effect of insulin, either because the hormone acts through the vagus centers or because continuous acetylcholine liber-

ation at the vagus endings is indispensable for this action of the hormone. Possibly the increased gastric motility is at least partly responsible for the sensation of hunger caused by insulin. This hormone also augments the peristalsis of the duodenum and colon but these latter actions are less conspicuous.

Severe overdosage with insulin, especially in the fasting subject, tends to cause acute gastric erosions, often accompanied by hemorrhages into the stomach. This effect is likewise prevented by glucose administration.

Skin and Appendages. — Trophic disturbances in the skin and its appendages are less common following pancreatectomy in experimental animals than in diabetic patients. However, pancreatectomized dogs tend to lose their hair and are subject to skin infections. This may partly be due to a secondary (relative) vitamin or lecithin deficiency. Insulin overdosage causes pallor of the skin and sweating in man.

Urinary System. — Neither pancreatectomy nor insulin overdosage cause any very obvious changes in the urinary system, except the tendency towards glycogen deposition in the convoluted tubules, sometimes noted following ablation of the pancreas.

Accessory Sex Organs.— After pancreatectomy, as well as following chronic insulin overdosage, the accessory sex organs tend to involute and the estrus cycle becomes irregular in experimental animals. Often continuous diestrus sets in. These changes are secondary to the involution of the gonads, which in turn is probably due to the general-adaptation-syndrome evoked by these severe metabolic disturbances.

Various Other Effects. — Regeneration and wound healing are markedly impeded by pancreatectomy but restored almost to normal by adequate insulin treatment. Lecithin and vitamin supplements have been assumed to cause further improvement. The rôle of insulin in regeneration, wound healing and resistance to infection has not been completely elucidated as yet. It is possible, however, that the hormone raises the ability of the damaged tissues to utilize glucose as a readily available source of energy for the metabolic processes involved in regeneration and local defence reactions.

INSULIN CONTENT OF BODY FLUIDS AND TISSUES

Various technics have been used to study the metabolism of insulin, that is, the mechanisms by which it is manufactured in the pancreas and subsequently disposed of, by the body.

The insulin content of the pancreas has been determined by acid aqueous-alcohol extraction of the hormone from the minced glands of various animal species. After purification, this extract may be standardized by any reliable bioassay technic (see "General Pharmacology" on p. 485) but it must be kept in mind that both the quantitative extraction and the bioassay of the hormone are subject to a number of unavoidable technical errors. Using this extraction method, it has been estimated that per gm. of tissue, the NORMAL PANCREAS of the dog contains about 4 units in the free splenic end, 3 units in the attached duodenal portion and 2 units in the free duodenal end. The insulin content of the normal human pancreas averages about 2 units per gm.

Methods for the direct estimation of *the insulin content of systemic* BLOOD are too unreliable to be of real value in hormone metabolism studies, but samples taken directly from the pancreatic veins contain sufficient amounts of insulin to be assayed with some measure of accuracy

quired to excrete the excessive quantities of glucose.

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alone effects a speedy restoration to normal. It is assumed that starvation, a high fat diet and insulin administration "rest" the islets, that is, decrease the necessity for insulin production. It must be repeated, however — as has been said with regard to other glands — that the concentration of a hormone within a gland is not necessarily an indication of hormone production; the diminution may be the result of increased discharge or decreased production.

TRANSPLANTATION OF SEVERAL PANCREASES, onto the neck of normal or pancreatectomized dogs, does not cause hyperinsulinemia since, as we shall see later, the regulation of insulin secretion is mainly humoral and independent of the nervous system.

NERVOUS STIMULI exert no very pronounced influence upon insulin secretion. As stated above, the blood sugar of a pancreatectomized animal is maintained at an approximately normal level by a transplanted pancreas introduced into the carotid-jugular circulation. The subsequent introduction of several more pancreases, with the consequent increase in insular tissue, causes no further change in blood sugar concentration. Since these transplanted pancreases are necessarily devoid of any extrinsic innervation it may be concluded that the nerves which reach the pancreas from the outside, exert no indispensable influence upon its hormone production. However, stimulation of the vagus appears to cause insulin secretion and, indeed, some investigators claim to have traced the corresponding pathways to the hypothalamic nuclei. These findings require confirmation, but in any event, the two observations are not necessarily contradictory. It is quite conceivable that the vagus stimulates insulin secretion but that another — presumably humoral — mechanism may in itself suffice for the gross regulation of insulin production. It should also be kept in mind that the "neuro-insular complexes" and ganglia within the pancreas could exert some nervous regulatory function which would not be eliminated by transection of the pancreatic nerves.

Administration of GLUCOSE — especially in the form of an injection into the pancreatic artery — increases insulin secretion. This is further proof that pancreatic hormone secretion is under humoral control.

ALLOXAN, which causes degenerative changes in the pancreatic islets, simultaneously diminishes their insulin content.

PHLORIDZIN decreases insulin secretion as shown by transplantation of the pancreas of phloridzin-treated dogs upon pancreatectomized recipients.

STIMULI INFLUENCING PANCREATIC STRUCTURE

Extirpation of Endocrine Glands. — HYPOPHYSECTOMY causes no constant, characteristic change in the structure of the Langerhans islets This observation speaks strongly against the assumption that the endocrine elements of the pancreas are under the control of a trophic anterior-lobe hormone, in the manner in which the adrenal cortex, thyroid or gonads are under the influence of the corresponding trophic pituitary principles

PARTIAL PANCREATECTOMY elicits a compensatory hypertrophy of the Langerhans islets in the remnant if an adequate amount of glandular tissue is left behind On the other hand, following ablation of about 70 to 90% of the pancreatic tissue, the islets in the remnant undergo a progressive degeneration; this affects primarily the insulin producing β-cells. Simultaneous administration of high carbohydrate diets accelerates this degenerative change,

The blood sugar variations of the experimental animal itself have also been used as an approximate indication of insulin production. Other important blood sugar regulating mechanisms may be eliminated in such studies by preliminary extirpation of the pituitary, the adrenals or the sympathetic nervous system. Yet, in view of the numerous factors (especially the hepatic homeostatic mechanism), which influence the blood sugar, such studies must be viewed very critically.

It is especially noteworthy that of all the endocrine glands, only the pancreas is situated in the portal circulation, so that insulin reaches the liver before it could affect any other organ. This, as well as the results of intraportal injections of insulin, has been interpreted to signify that hepatic detoxification plays no important rôle in insulin metabolism and that probably the hormone reaches the liver first because its main action is exerted upon this organ.

The normal URINE contains no detectable quantities of insulin.

ADRENALECTOMY or HYPOPHYSECTOMY does not change the insulin content of the pancreas significantly

PARTIAL PANCREATECTOMY does not alter the insulin content of the (dog) pancreas, providing that sufficient islet tissue is left to prevent the development of degenerative changes in the β-cells and diabetes Extensive partial pancreatectomy, which leads to hydropic degeneration of the β-cells and the Sandmeyer type of diabetes, causes a sudden and pronounced decline in the insulin content of the pancreas.

The hyperglycemia produced by ADRENALINE appears to call forth a compensatory insulin secretion as judged by various bioassay technics

No changes in pancreatic insulin content (rat) could be demonstrated, following treatment with CORTICOID extracts. However, these experiments will have to be repeated with purified gluco-corticoids.

Certain ANTERIOR-PITUITARY EXTRACTS increase the insulin content of the (rat) pancreas as well as the islet volume. As stated elsewhere it is doubtful, however, whether these effects should be regarded as due to a special *pancreatotrophic hormone.*

Purified *luteotrophin* (prolactin) raises the insulin content of the pancreas both in the normal and in the hypophysectomized rat.

Somatotrophin (growth hormone) diminishes the insulin content in normal as well as in adrenalectomized animals, but curiously, this effect is not demonstrable after hypophysectomy.

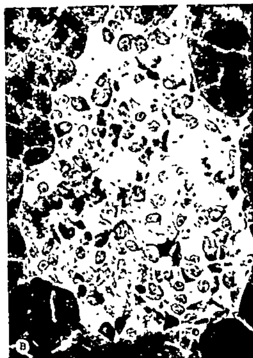
Administration of partially purified *diabetogenic anterior-pituitary extract* first causes a marked stimulation of the islets, but at a later time results in degenerative changes accompanied by a decrease in their insulin content.

Daily injections of INSULIN decrease the insulin content of the (rat) pancreas, probably as a manifestation of a compensatory inhibition of hormone secretion.

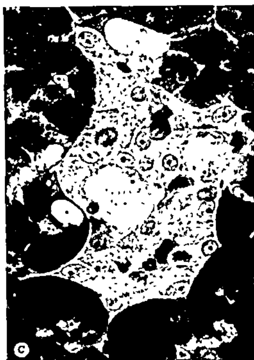
FOLLICULOIDS augment the insulin content of the (rat) pancreas but only in the presence of the hypophysis.

In CLINICAL DIABETES, the insulin content of the pancreas is extremely variable, the average value being about 0 4 units per gm., that is one-fifth of the normal Further studies will be required, however, to differentiate between the various extra-pancreatic and pancreatic types of diabetes in man The insulin content of Langerhans-islet-tumor tissue is exceedingly high Thus, in one case, it was more than 210 units per gm

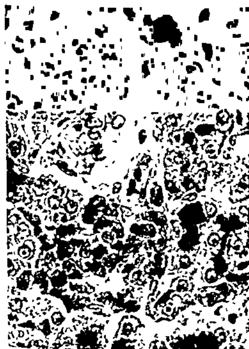
Fasting, or DIETS rich in fat, diminish the insulin content of the pancreas to about half the normal value, which is approximately 2 5 units in the rat. Subsequent return to a normal diet or even administration of carbohydrate



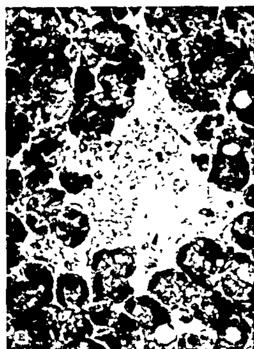
— B. Islet from permanently diabetic dog Note loss of beta-cell granules in majority of cells, complete degranulation on the left of islet, some granules remaining on the right and towards the center. Alpha-cells unaffected (X 750)



— C. Islet from permanently diabetic dog Note hydropic degeneration of individual beta-cells. However, often anterior-pituitary extracts cause diabetes without eliciting islet damage (X 1300)



— D. This islet is reduced to a group of alpha-cells (dark clump on lower side of field) The rest of the islet area is hyalinized and hence homogeneous (X 1000)



— E. Completely hyalinized, homogeneous islet (X 550)

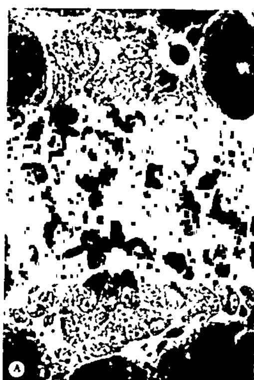
(Courtesy of Drs K C Richardson and F G Young)

which is interpreted as a sign of exhaustion. It forms the basis of the so-called "Sandmeyer diabetes" (see p. 490). Correspondingly, partial starvation or low carbohydrate diets tend to protect the remaining β-cells by diminishing the "overstrain."

OBSTRUCTION OF THE PANCREATIC DUCTS by ligature causes pressure atrophy of the acinar tissue without significantly influencing the Langerhans islets. In most species, the pancreas has several excretory ducts, all of which must be obstructed in order to make this intervention successful. Some investigators reported that pancreatic duct ligature actually enlarges the islets but these claims did not remain unchallenged.

INJECTION OF IRRITATING SUBSTANCES INTO THE PANCREATIC DUCT (e.g., trypsin, bile, emulsions of bacteria) may cause acute pancreatitis, with subsequent pancreatic necrosis, affecting both the *acinar and islet tissue*

ADRENALECTOMY, PARATHYROIDECTOMY, THYROIDECTOMY AND CASTRATION (in either sex), cause no constant morphologic changes in the pancreas.



Changes in the Langerhans Islets of a dog rendered permanently diabetic with prolonged anterior-pituitary extract treatment. — A. Normal islet from control dog Alpha-cells with dark granules, beta-cells with paler granules. Blood corpuscles and capillaries are stained opaque black. (X 1300) (Cont'd on p 503)

Hormones. — ANTERIOR PITUITARY EXTRACTS exert a pronounced effect upon the structure of the Langerhans islets As previously stated, the evidence favoring the assumption of a special "pancreatrophic" (or "pancreatotrophic") hormone is not convincing. It has been stated that in the rat, fol*lowing injection of certain anterior-lobe* extracts, the quantity of islet tissue may increase. At the same time numerous mitotic figures appear and the insulin content of the pancreas rises However, if such treatment be continued over a longer period, degranulation and hydropic degeneration of the β-cells ensues, with subsequent destruction of the islet tissue. In view of the repeatedly mentioned fact that hypophysectomy occasions no noteworthy islet atrophy, it is probable that the above-mentioned changes are not due to a special "trophic" factor but are caused by the action of the diabetogenic or glycotropic (insulin antagonizing) anterior-lobe principles which raise the demand for insulin, and thus eventually cause an "exhaustion atrophy" such as is seen in Sandmeyer's *diabetes.*

Prolonged treatment with INSULIN causes progressive compensatory atrophy of the islets and especially of their β-cells. It is rather difficult to understand, however, why certain investigators obtained hyperplasia of the islets in insulin-treated animals

THYROID HORMONE has a very pronounced stimulating effect upon the development of the acinar tissue and thus increases the weight of the pancreas. Moderate doses of thyroxin have also

development of diabetes in thyrotoxic patients. It will be recalled, however, that thyrotoxicosis leads to a decrease in the glycogen-forming ability of the liver; this in itself may explain the impaired sugar tolerance which so often accompanies this disease.

Hyperplasia of the Langerhans islets is rare in thyrotoxicosis but, if present, it may represent an attempt to compensate for the impaired glucose-tolerance.

Diet. — While STARVATION causes inconsistent changes in the structure of the Langerhans islets, OVER-EATING accompanied by adiposity, may lead to multiple foci of fat necrosis in the pancreas, these are very common, especially in fattened swine.

High CARBOHYDRATE diets cause degranulation of the β-cells, presumably a sign of a compensatory increase in insulin secretion.

Nervous Stimuli. — Lesions in the HYPOTHALAMUS may lead to hydropic degeneration of the Langerhans islets in the rhesus monkey.

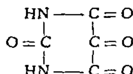
Following VAGUS stimulation, the outlines of the cell cords in the Langerhans islets may become indistinct with vacuolization of their cytoplasm. Changes in the histologic structure of the islets have also been reported following vagotomy and after stimulation or destruction of the SPLANCHNIC fibers, which innervate the pancreas. All these lesions have been thought to indicate that the nervous system exerts an important influence upon the endocrine elements of the pancreas, although the nature of this action remains obscure

Age. — The amount of islet tissue, per Kg. of body weight, is usually greater in immature than in adult animals. During the first year of life, the number of islets, per visual field, decreases in man and the individual variation in islet size is greater during the first year than later Yet, the islet tissue continues to proliferate after birth and its absolute mass is greater in the adult than in the newborn.

Pregnancy. — During gestation, the Langerhans islets are more developed than otherwise and show histologic signs of increased activity.

Drugs. — PHLORIDZIN (see: p. 491) causes renal diabetes and tends to produce hyperplasia, especially of the β-cells in the islets, however, this effect is not very constant.

Among the drugs, ALLOXAN has the most specific effect upon the islet tissue. The formula of alloxan is the following:



A single dose of this compound suffices to cause β-cell degeneration and finally complete necrosis of the Langerhans islets, which results in a special type of pancreatic diabetes. This effect has now been noted in a number of animal species, including man, but the mechanism of alloxan action is still unexplained. The frank diabetes (due to deficient insulin production) of alloxan treated animals is usually preceded by an initial hyperglycemia, followed by a decrease in blood sugar (obtainable even after pancreatectomy). The effect of the drug is not entirely limited to the islets, since it also causes lesions in the adrenals, heart and liver In birds, it produces urate depositions reminiscent of gout. The cells of spontaneous islet-cell adenomas are usually resistant to alloxan

Rays. — Animal experiments indicate that mild doses of X-rays may cause a hyperplasia of the Langerhans islets with some degree of hypoglycemia, while heavy overdosage results in degenerative changes and involution both of the acinar and of the islet tissue Marked X-ray damage to the pancreas can produce diabetes

been claimed to augment the size of the islets. On the other hand, severe overdosage *with thyroxin, especially* in partially pancreatectomized animals, or in those pretreated with anterior pituitary extracts, causes degeneration of the β-cells with the appearance of diabetes. Apparently, partial inactivation of the pancreas is necessary before the thyroid hormone overdosage can cause sufficient "overstrain" to induce islet degeneration *(Houssay et al.)*. The resulting diabetes may last only as long as the thyroid hormone is administered (thyroid diabetes), but in severe cases it becomes permanent and persists after discontinuation of thyroid hormone treatment (metathyroid diabetes).

No other hormone preparation has been shown to elicit any characteristic morphologic changes in the Langerhans islets; even SECRETIN, in doses which cause exhaustive stimulation of the acinar cells with depletion in zymogen granules, produces no consistent change in the islets.

Diseases. — In ACROMEGALY the pancreas may be enlarged or atrophic. Similarly, the islet tissue may be overdeveloped or undergoing hydropic degeneration. This inconsistency is reminiscent of the actions of anterior-lobe extracts which, as we have seen, may also cause stimulation or degeneration of the islets, depending upon experimental conditions The comparatively frequent association of diabetes with acromegaly may, in some instances, be ascribed to secondary degeneration of *the islets.* CUSHING'S DISEASE can likewise be accompanied either by enlargement or atrophy of the islets.

In SIMMONDS' DISEASE the pancreatic islets are usually normal.

In DIABETES MELLITUS significant degenerative changes in the islets are far from constant. In a large number of diabetics, the islets undergo various types of degenerative (hydrops, hyalinization, cirrhosis, simple atrophy, arteriosclerosis of the vessels with consequent scar formation) or inflammatory changes; indeed, in some instances, complete or subtotal destruction of the pancreatic tissue by tumors, inflammations, necrosis, etc., has been shown to be the cause of diabetes. In many instances, however, the islets are of normal appearance and we must either assume a purely functional disturbance or an extrapancreatic (e.g., hypophyseal) type of diabetes.

In children, diabetes is usually accompanied by hydropic degeneration or hyalinization of the islets. (See also "Pathologic Anatomy of Diabetes Mellitus, on pp. 509, 510.)

In FETUSES OF DIABETIC MOTHERS, the Langerhans islets are often greatly enlarged. This has been interpreted as a sign of compensatory hypertrophy, in an effort to combat the insufficiency of the maternal organism.

In BRONZE DIABETES there is hemosiderosis and cirrhosis of various organs, especially the liver and the pancreas The cirrhosis is generally regarded as a consequence of the hemosiderin depositions, although in certain conditions (e.g., pernicious anemia), hemosiderosis does not lead to cirrhosis. In any case, the pancreas in bronze diabetes is intensely pigmented and the accompanying hyalinization and cirrhosis of the islets is probably an important contributory factor, if not the main cause, of the disturbance in carbohydrate metabolism

THYROTOXICOSIS in man is usually unaccompanied by any characteristic change in the Langerhans islets. In some instances, however, the pancreatic stroma proliferates and the islets undergo sclerosis, lymphocytic infiltration or even partial necrosis. These lesions are reminiscent of those produced by thyroid hormone overdosage in experimental animals They may be a contributing factor in the comparatively frequent

DISEASES OF THE PANCREAS

MALFORMATIONS

Congenital anomalies of the pancreas are rarely the cause of endocrine derangements. Anomalies in the rotation of the gut during embryonic development may result in ANNULAR GLANDS which surround the intestine, or lead to INCOMPLETE FUSION of the dorsal and ventral primordia.

ECTOPIC PANCREATIC TISSUE may develop from anomalous origins of the primordia at almost any point along the gastrointestinal tract.

Complete APLASIA, true HYPOPLASIA or HYPERPLASIA of the Langerhans islets has never been proven to occur as a malformation.

DEGENERATIONS

Severe degenerative changes of the Langerhans islets are invariably accompanied by diabetes; they are discussed on pp. 509, 510. The most important pertinent lesions are HYALINIZATION, HYDROPIC DEGENERATION with VACUOLIZATION and SCLEROSIS If only a small number of Langerhans islets are affected by any of these changes, the remaining endocrine tissue completely compensates for the loss and there are no clinical manifestations of diabetes Suffice it merely to mention such extraordinarily rare degenerative changes as AMYLOIDOSIS and infiltration with GLYCOGEN The so-called LIPOMATOSIS OF THE PANCREAS is only a local manifestation of general obesity The fat is contained mainly in the stroma, but, if excessively developed, a considerable pressure atrophy of the parenchyme may result

INFLAMMATIONS

Acute Hemorrhagic Pancreatitis and Pancreatic Necrosis. — In severe cases of this disease, the pancreas is enlarged, friable and soft. Multiple hemorrhages and white "fat necroses" usually give the organ a mottled aspect The white patches of "fat necrosis" are due to hydrolysis of fat and liberation of fatty acids by activated pancreatic enzymes. Calcium is subsequently deposited because insoluble calcium-fatty-acid soaps precipitate in the affected areas. True inflammatory changes are usually secondary to the above-mentioned disturbances.

The ETIOLOGY of this condition is still obscure. It may be reproduced in experimental animals by the injection of bile or other irritating materials into the pancreatic duct. It has therefore been assumed that, at least in some cases, a regurgitation of bile and activated pancreatic juice into the gland may digest its substance and thus produce necrosis. Other investigators believe that a vascular lesion is the primary factor and that the necrosis is secondary to nutritional disturbances. The more common organisms found in such pancreases are Streptococcus and Bacillus coli, but microbial invasion is probably also secondary to nutritional disturbances which decrease the resistance of the tissue

CLINICALLY, acute hemorrhagic pancreatitis is characterized by a sudden onset with severe epigastric pain, often but not always, associated with various gastrointestinal manifestations, especially nausea and vomiting In most instances, the condition progresses rapidly towards shock, coma and death within about 48 hours

Acute Interstitial Pancreatitis. — This is a comparatively rare condition, characterized by inflammatory lesions around the ducts, usually due to an infection ascending through the latter. It is not infrequently accompanied by similar lesions in the salivary glands, some apparently pertinent cases may be hematogenous and represent modified types of mumps. There is intense fibrosis and scar formation in the stro-







Effect of alloxan on Langerhans Islets (Rat). — **A.** Langerhans islet in the pancreas of a normal control rat Note appearance of the intact beta-cells which contains dark granules — **B.** Tissue taken 24 hours after the injection of alloxan Note complete disintegration of the dark-staining beta-cells, while the alpha-cells (in periphery) are well preserved — **C.** Note complete disappearance of degenerated beta-cells in a specimen taken 120 hours after alloxan injection.

(Courtesy of Dr G Gomori)



Accessory pancreas. Aberrant pancreatic tissue in jejunum Villosities of intestinal mucosa and individual (light) Langerhans islets in pancreas are distinguishable, even at this low magnification

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CLINICALLY, acute hemorrhagic pan*creatitis* is characterized by a *sudden* onset with severe epigastric *pain*, often but not always, associated *with* various gastrointestinal *manifestations*, especially nausea and vomiting. In most instances, the condition progresses rapidly towards *shock, coma and death* within about 48 *hours*.

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ma and the ducts are filled with a mucopurulent exudate. In very acute cases. hemorrhagic pancreatitis may result, but more frequently, the lesions heal with scar formation and are merely *incidental* findings at autopsy.

Chronic Pancreatitis. — In this condition, the acini are atrophic while the stroma is fibrous and excessively developed. The lesion is more reminiscent of a cirrhosis than of an inflammation and has been regarded as due to repeated mild attacks of acute pancreatitis.

DIABETES MELLITUS

Terminology. — If the disease is due primarily to a pancreatic disturbance, we call it pancreatic diabetes or hypoinsulinism Types due to pituitary disturbance (hypophyseal diabetes), or primary adreno-cortical disturbance (adrenal diabetes), should be regarded as distinct disease entities.

DEFINITION

Diabetes mellitus is a condition, mainly characterized by persistent hyperglycemia and glycosuria. It is generally assumed though not proven, that the common type of diabetes mellitus is primarily an insufficiency in the insulin production of the pancreas. This may be due to a primary failure of hormone production by the Langerhans islets (*e g., destruction by tumors, inflammations*), or to their secondary breakdown resulting from excessive stimulation by anterior-pituitary hormones (e.g., in certain types of anterior-lobe tumors and hyperplasias). In clinical medicine it is not always possible to distinguish sharply between the two types.

The adreno-cortical diabetes is considered in the section on the adrenals, since its pathogenesis differs essentially from that of the common diabetes mellitus The so-called renal glycosurias are due to a decreased renal threshold for glucose, usually accompanied by hypo- or normo-glycemia and must be clearly distinguished from true diabetes.

CLASSIFICATION

The clinical types of diabetes mellitus may be classified according to various points of view.

According to the AGE OF ONSET we distinguish:

(1) *Infantile and juvenile diabetes*
(2) *Adult diabetes.*
(3) *Senile diabetes.*

This classification is justified since the usual course of the disease is largely dependent upon the age at which it commences. Infantile and juvenile diabetes tend to be rapidly progressive and lead to acidosis with cachexia but rarely to diabetic gangrene or skin infections. The characteristic features of diabetes in children may be partly due *to the marked somatic growth urge and* the rarity of accompanying cardiovascular "diseases of adaptation" in very young patients.

In young adults and middle-aged people, diabetes may or may not lead to cachexia and is frequently accompanied by adiposity.

In senile individuals, the progress of the condition is slow and there may even be spontaneous regressions The cachectic type of diabetes is rare at this age and the cardiovascular manifestations, especially gangrene and trophic disturbances, are more prominent.

According to the INTENSITY OF THE DISEASE we may distinguish:

(1) *Latent or potential diabetes*, in which the fasting blood sugar does not exceed 100 mg.% and glycosuria subsides after slight dietary restrictions. Even after meals the blood sugar does not rise above 170 mg.%

(2) *Mild diabetes*, in which the hyperglycemia (*which may be quite* marked), is promptly corrected by a

restriction in food intake, sufficient to cause some reduction in weight. As a general rule it is stated that "every untreated overweight diabetic patient has a mild diabetes." Of course, the slightly abnormal glucose tolerance curves of obese patients are not necessarily indicative of diabetes.

(3) *Severe diabetes*, in which hyperglycemia is accompanied by a marked tendency to ketosis and coma. Even if the blood sugar level does not exceed 250 mg.%, the diabetes is usually severe if the patient is underweight before the initiation of treatment.

According to the STATE OF NUTRITION, it is customary to distinguish types, which often merely represent stages in the course of the disease :

(1) *Fat diabetes*, with a tendency to be overweight even without insulin treatment.

(2) *Lean diabetes*, with a tendency to lose weight in the absence of hormone treatment.

This classification is somewhat reminiscent of the former, inasmuch as, among untreated cases, the fat diabetic usually has a mild, and the lean patient a severe type of diabetes The relationship between the blood sugar and the patient's weight (and response to dietary measures), is a better indication of the severity of the condition than the fasting blood sugar level.

According to INSULIN SENSITIVITY we distinguish :

(1) The *insulin sensitive* type, which requires only minimal amounts of insulin to prevent glycosuria

(2) The *insulin insensitive* (or insulin resistant) type, whose blood sugar is controlled only by considerable doses of *insulin*; indeed, in some instances the resistance to insulin is almost complete

The clinical syndrome of diabetes may also be subdivided according to the underlying ETIOLOGIC FACTORS (see p. 512), the predominant MORPHOLOGIC LESIONS (see: Pathologic Anatomy), or into simple and complicated diabetes, according to the presence or absence of COMPLICATIONS (see· p. 524).

PATHOLOGIC ANATOMY

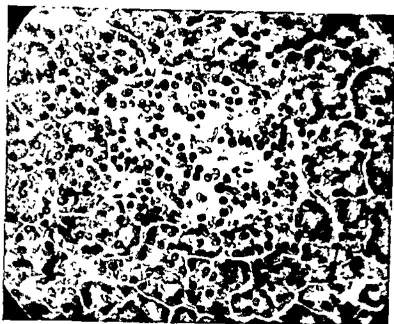
Until quite recently it was *difficult* to explain why the pancreas of so many diabetics shows NO ANATOMIC LESION which could explain the disturbance in carbohydrate metabolism. Now we know, however, that certain anterior-pituitary and adreno-cortical extracts can cause diabetes in experimental animals without the production of Langerhans islet lesions. It is quite possible therefore, that in the absence of a Langerhans islet change, hypophyseal or adreno-cortical hyperactivity may also be the cause of spontaneous diabetes in man

Even if morphologic lesions in the *pancreas are demonstrable, their* character is not always the same

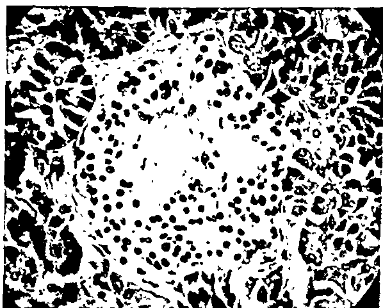
HYALINIZATION of the Langerhans islets is the most common pancreatic lesion in diabetes mellitus It consists of the chronic production of hyalin masses which gradually destroy the epithelial cells of the islets The hyalin material is intercellular, developing in the proximity of the blood vessels and apparently destroying the islet cells by compression The hyalin mass may eventually become larger than the normal islet This change is most common in middle-aged and elderly diabetics

FIBROSIS is also a chronic process, here fibrous tissue gradually replaces the islet cells This is generally viewed as a chronic type of pancreatitis and is found in about 25-50% of the diabetics. Like hyalinization, it occurs most frequently in patients over 40 years of age.

HYDROPIC DEGENERATION is usually a more acute process, most commonly found in juvenile diabetics. In the early stages, the granules of the β-cells disappear and are gradually replaced by



Normal Langerhans islet (Man).



Langerhans islet in diabetes. Note replacement of Langerhans islet cells by *hyaline material*
(Courtesy of Dr R T Waugh)

vacuoles Eventually the hydropic degeneration extends to all the cells of the islets and destroys them. The lesion is reminiscent of that seen in the pancreatic remnant of animals subjected to very extensive pancreatectomy. This change is probably due to exhaustion of the islets, especially since insulin therapy tends to counteract it.

ROUND-CELL INFILTRATION of the Langerhans islets occurs especially in young, severe diabetics and leads to the rapid progressive destruction of the endocrine tissue.

ACUTE PANCREATITIS rarely causes diabetes (see. p. 507).

Destruction of the pancreas by TUMORS is a very exceptional cause of



Diabetes due to multiple pancreatic calculi. 50-year-old man, with multiple pancreatic calculi (arrows). Complained of symptoms for 15 years; suffers from diabetes mellitus, deficiency of external secretion of pancreas with steatorrhea and enlargement of the liver. Diabetes following pancreatic atrophy due to calculi is rare
(Courtesy of Dr E H Mason)

diabetes. Almost the entire pancreatic tissue must be involved before diabetes occurs and such an extensive infiltration is rarely compatible with life.

Arteriosclerosis and other VASCULAR LESIONS are common accompaniments of diabetes, in pertinent cases it is sometimes difficult to establish whether extensive scar formation with arteriosclerosis in the pancreas is the cause, or the result of diabetes

Among the less common morphologic findings in the pancreas of diabetic patients, we may also mention : extensive PYKNOSIS of the Langerhans islet nuclei, SYPHILITIC FIBROSIS and gumma formation, LIPOMATOSIS of the pancreas with extensive fat infiltration, OBSTRUCTION OF THE PANCREATIC DUCT due to pressure from without (neoplasms, inflammations), or within (pancreatic calculi) followed by inflammatory changes and fibrosis in the gland, and occasionally, so-called "SIMPLE ATROPHY" of the islets without any obvious cause

In some instances, HYPERTROPHY AND ADENOMA FORMATION in the Langerhans islets have been seen in diabetics and were interpreted as due to compensatory regenerative phenomena.

The morphologic changes in organs other than the pancreas are considered, together with their functional disturbances (see : pp. 517-524).

INCIDENCE

Statistical studies indicate that there are more than half a million cases of diabetes in the United States and the incidence of this disease still shows a continuous upward trend It is estimated that approximately three million persons now living in the United States either have, or will develop diabetes. In Canada there are approximately 30,000 diabetics As a cause of death, diabetes took ninth place among all diseases in 1938 and accounted for approximately 2% of all deaths. It is generally recognized that diabetes is most prevalent among wealthy people, perhaps because overeating and sedentary occupations are important factors in its pathogenesis.

OCCUPATIONAL FACTORS appear to play an important rôle, inasmuch as the incidence of the disease is about

65% higher in the urban than in the rural communities. This may be due to the fact that rural populations are more given to occupations requiring physical exercise and less likely to develop obesity. Diabetic mortality is highest among merchants and lowest among laborers and farm workers.

Up to about 40 years of AGE, the death rates of diabetics are about equal for both SEXES, but later (at and after the menopause), the mortality rate of women rises much more rapidly than that of men. Between 55 and 65 years of age, the mortality rate of women is about 100% above that of men. Up to about 40 years of age, in the United States, the death rate per 100,000 population is less than 10 in either sex, while at 70 years of age, it is 125 among men and 230 among women. These figures clearly indicate the comparative rarity of diabetes in the younger age groups.

Lack of physical exercise, a tendency to obesity and disturbances in the endocrine balance may be the cause of the high incidence of diabetes among women during and after the menopause.

RACIAL AND HEREDITARY factors also play an important rôle. The *Jewish* race is especially predisposed to this disease, which is also common among the *Teutonic*, but comparatively uncommon among *Slav* and *Latin* races. It has been claimed that the mortality rate from diabetes is high among the *Irish* in the United States, but low in Ireland.

Contrary to the views of some early investigators, the *Negro* race is not immune to diabetes, although the incidence among them is comparatively low, perhaps because of their lower economic status. This may also explain the comparative rarity of diabetes among the *Chinese* and *Japanese*.

It may be considered as an established fact that diabetes is an *inheritable* disease. It follows a mendelian recessive pattern, on the basis of which it may be predicted whether diabetes will develop in the offspring of parents whose condition is known. It is of special importance that when both parents have diabetes, all of their children will eventually develop the disease, if they live long enough. When one parent is a diabetic, the other a carrier, 40% of the offspring may be expected to develop diabetes; if a diabetic patient or carrier marries an individual who neither has, nor is a carrier of diabetes, none of the children will develop the disease, unless they acquire an incidental disease of the pancreas. However, all the offspring from such a marriage will be carriers. The high incidence of diabetes in the Jewish race may perhaps be explained on the basis of inbreeding, heredity and occupation.

PATHOGENESIS

The various etiologic factors which play a rôle in the pathogenesis of diabetes mellitus have already been described above (see: "Pathologic Anatomy" and "Incidence"). There, we emphasized that a variety of pancreatic lesions — degenerative changes, inflammations or even tumors — may be the immediate cause of the disturbance in carbohydrate metabolism. We also saw that certain occupations, age, sex, race, heredity and the state of nutrition of the patient are important predisposing factors. In other cases, a condition practically indistinguishable from pancreatic diabetes may develop as the result of a deranged pituitary or adreno-cortical activity.

Only rarely is diabetes due to destruction of the pancreas by an acute, local inflammatory or neoplastic disease. In the vast majority of the cases, the disturbance develops in a hereditarily predisposed individual under the influence of factors which throw an

excessive load upon the endocrine balance. Frequently it results from chronic pancreatitis secondary to cholelithiasis and the regurgitation of bile into the pancreas.

The pathogenesis of the metabolic disturbances in diabetes, have been discussed in connection with the "Mechanism of Insulin Action." (See p 487.)

CLINICAL COURSE

State. — Diabetes mellitus, especially in its early stages, is not characterized by typical clinical manifestations. It is estimated that about 12% of all diabetics are not diagnosed until sugar *is accidentally found in the urine during* a routine check-up.

The most characteristic complaints of the patient are : almost continuous fatigue, polyuria, polydipsia and polyphagia often, but not always accompanied by a loss of body weight

Not infrequently, various types of neuralgias, paresthesias, pruritus and complicating skin infections or cardiovascular disturbances are among the presenting symptoms The notoriously low resistance of diabetics to various types of INFECTIONS is of particular importance Such patients frequently suffer from intercurrent infections of the respiratory passages (e g , tracheitis, bronchitis, broncho-pneumonia and especially pulmonary tuberculosis) Conversely, intercurrent infectious diseases tend to aggravate the diabetes and to raise insulin requirements

Metabolism. — Diabetes mellitus does not produce any consistent change in the B M R. The latter may be normal, *elevated or subnormal* In general, however, the R Q is low in untreated cases because of the impairment in carbohydrate combustion, or increased gluconeogenesis

Carbohydrate Metabolism. — The BLOOD SUGAR is elevated and values of more than 120 mg % after 8-14 hours fasting, or over 160 mg % postabsorptive, are pathologic. There is practically no difference between the fasting glucose concentration in arterial and venous blood, a fact which has (perhaps incorrectly), been considered indicative of a diminished glucose utilization by the peripheral tissues. Normally, arterial blood contains more glucose than venous blood owing to the utilization of sugar by the tissues.

Various tests have been devised for the detection of comparatively mild impairments in glucose tolerance. In using these tests it is important to keep in mind that the previous nutrition of the patient exerts a marked influence *upon them* It is *generally recommended*, therefore, that for three days before a glucose tolerance test, the patient should take at least 300 gm of carbohydrates per day, since a low carbohydrate intake during the days preceding the test would diminish carbohydrate tolerance

One of the most commonly used procedures is the glucose tolerance TEST OF EXTON-ROSE This is performed as follows

100 gm of glucose dissolved in 650 cc of water is flavored with lemon juice and divided into two equal parts After fasting overnight, the patient empties his bladder Then venous blood is taken for sugar determination and immediately afterwards, the first portion (50 gm. of glucose) of the sugar solution is ingested. After an interval of 30 minutes a second blood sample and a urine specimen are taken for analysis and the remaining half (50 gm of glucose) of the sugar solu*tion is ingested* Blood and urine are obtained for the third time following another 30 minute interval.

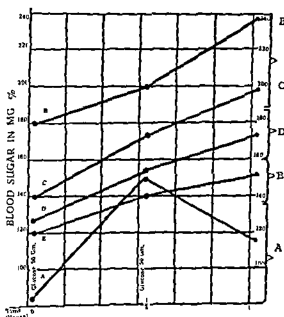
Since this test is usually performed in doubtful cases, the fasting blood sugar values are often normal. The most important data are obtained in the second half hour of the test and major emphasis is placed upon the

comparison of the blood sugar values at the end of the first and second half hours. In normal individuals the fasting blood sugar level is below 120 mg.%, the one hour level does not exceed 160 mg.% and the blood sugar is lower at the end of one hour than at the end of 30 minutes. There is no glycosuria at any time.

Conversely, in diabetics, even though the fasting value may be normal, at the end of one hour the blood sugar rises above 160 mg % and frequently the urine contains sugar A continued increase in blood sugar of more than 25 mg.% occurs between the 30 minute and one hour determination.

The test is an important aid in diagnosing diabetes but the general condition of the patient, especially the presence of an infection (which tends to decrease sugar tolerance,) must always be kept in mind. The severity of the diabetes is more accurately estimated by the persistence of hyperglycemia during fasting, the response to insulin treatment and to reduction in caloric intake, as well as the body weight before treatment. As stated above, mild cases show a considerable improvement following mere reduction of the food intake and patients who are obese before the administration of insulin, may generally be considered mild.

Results of the One-Hour Two-Dose Glucose Tolerance Test (Exton-Rose Procedure)



(From G G Duncan *Diseases of metabolism* W B Saunders Co Philadelphia, London)

Note — A, the normal curve, note rapid rise and prompt fall of the blood sugar level. B and C, characteristic of diabetes, note the continued increase in the sugar concentration with fasting values above normal Curve D represents presumptive diabetes and curve E presumptive normal, both are nondiagnostic

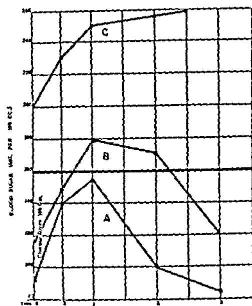
The STANDARD ONE DOSE TEST is performed as follows:

After fasting overnight, a sample of blood is taken for sugar determination and the bladder is emptied. Following this, 100 gm. of glucose dissolved in 300 cc. of water flavored with lemon juice, is ingested. Additional specimens of blood and urine are taken for sugar determination, 30 minutes, 1, 1½, 2 and 3 hours later.

In normal individuals the fasting blood sugar level does not exceed 120 mg.%, reaches its peak within 30 minutes and returns to normal within 1½ hours after the glucose ingestion. The actual height of the blood sugar peak is of no great importance as long as it is below 180 mg %. The initial blood sugar value may be normal even in diabetic individuals, but in them, glycosuria tends to occur and the arterial glycemia exceeds 180 mg.% at some time during the test, not returning to normal even 3 hours after sugar ingestion

Both these tests are based upon the decreased sugar tolerance of diabetics. The Exton-Rose test rests particularly upon the absence of the Staub-Traugott effect, which produces a drop in blood sugar, after the second dose of glucose, in normal individuals In the standard one dose test, the decreased glucose tolerance reveals itself by delayed disappearance of glucose from

Three Glucose Tolerance Curves (Standard One-Dose Test)



(From G. G. Duncan, *Diseases of metabolism* W. B. Saunders Co. Philadelphia London)

A depicts the normal glycemic response to the oral administration of 100 gm. of glucose. The rise in the blood sugar level is rapid but a normal value is restored in two hours. In B, the glycemic response is slower and normal values are not restored until the third hour as is found in mild diabetes. C depicts the fasting hyperglycemia and the continued increase in the blood sugar level, even at the third hour, as seen in severe diabetes. Glycosuria usually occurs when the blood sugar level is maintained (for several hours) above 160 mg. per 100 cc. as depicted by the heavy black line.

the blood and the appearance of glycosuria because the blood sugar level is maintained for several hours above the threshold of 160-180 mg.%. In the normal individual no glycosuria occurs since the blood sugar does not rise above this threshold level.

The INTRAVENOUS DEXTROSE TOLERANCE TEST is recommended (*Soskin* et al.) in order to differentiate between mild diabetes and hepatic insufficiency, which tend to give similar curves in other tolerance tests. It is based upon the observation that intravenously injected dextrose causes a greater and more persistent hyperglycemia in diabetics, than in patients with liver disease.

The presence of sugar in the urine or the development of a fasting hyperglycemia are not in themselves, necessarily diagnostic indices of diabetes mellitus, since a number of other conditions (see "Diagnosis", on p. 525) may also produce them.

Lipid Metabolism. — As carbohydrate utilization becomes progressively more impaired, the diabetic organism is increasingly more dependent upon fat as a source of energy. The resulting increase in the intermediary fat metabolism may be one of the causes of the so commonly observed diabetic HYPERLIPEMIA. 100 cc. of normal plasma contains: 140-250 mg. cholesterol, 190-450 mg. total fatty acids, 0-370 mg. neutral fat, 60-350 mg. phospholipids, and 400-1400 mg.% total lipids. In diabetes the blood fat may rise so markedly that the plasma assumes an opaque, milky appearance and the total lipid concentration rises to 10% (in very unusual cases, even up to 25%[1]) of the plasma volume.

Hypercholesterolemia, hyperglycemia, glycosuria, ketonuria and acidosis do not necessarily develop simultaneously and to the same extent but, especially in untreated patients, the degree of hypercholesterolemia is an approximate index of the lipemia in general and to some extent, of the severity of the diabetes. Plasma cholesterol values of more than 1,000 mg.% are observed only in exceptional cases, but values of 250-400 mg.% are quite common. Even when adequate treatment depresses the blood sugar to within normal limits, the blood cholesterol may remain elevated for varying periods, yet insulin is highly effective in restoring the blood lipids to normal.

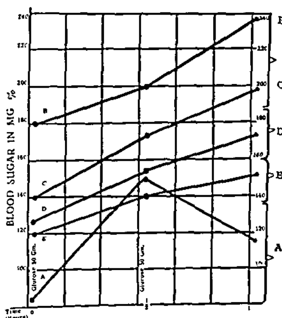
For unknown reasons, in the terminal stages of the disease, some diabetics develop hypocholesterolemia; this may or may not be accompanied by an

comparison of the blood sugar values at the end of the first and second half hours In normal individuals the fasting blood sugar level is below 120 mg.%, the one hour level does not exceed 160 mg.% and the blood sugar is lower at the end of one hour than at the end of 30 minutes There is no glycosuria at any time.

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The test is an important aid in diagnosing diabetes but the general condition of the patient, especially the presence of an infection (which tends

Results of the One-Hour Two-Dose Glucose Tolerance Test (Exton-Rose Procedure)



(From G G DUNCAN *Diseases of metabolism* W B Saunders Co Philadelphia London)

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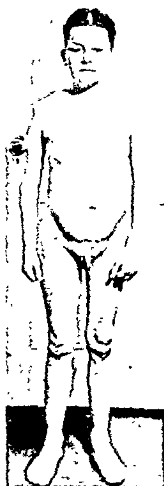
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duce ammonia is impaired. This, in combination with the increased formation of acid ketone-bodies, accounts for the diabetic acidosis. The degree of acidosis runs closely parallel with the decreased CO_2-COMBINING POWER of the plasma. When the latter falls to less than 15 volumes % (normal, 55-80%), coma almost invariably ensues, although there are individual variations; patients have been observed to go into severe coma with values of 28 volumes %, while others remained conscious, though drowsy, with values of 10-12 volumes %. In the pre-insulin era, 25 volumes % was regarded as the critical level from which recovery rarely occurs, but with the introduction of insulin, patients have been known to recover even when the plasma CO_2-combining power dropped to 2 volumes %. It is noteworthy that, as acidosis progresses, the patient becomes more and more insulin *insensitive*.

A large fraction of the acid ketone-bodies is eliminated in the form of their ammonium and fixed-base salts. The continued loss of fixed base, thus incurred, entails a reduction in the SODIUM and CHLORIDE concentrations of the blood and tissues, as well as a shift of the hydrogen ion concentration of the blood towards the acid side. Although the *plasma chloride and sodium* concentrations usually remain within normal limits, the polyuria and base loss finally tend to cause hyponatremia, and to a lesser extent, hypochloremia.

It is noteworthy that since reduction of base *is equivalent to* reduction of total electrolyte content in the body fluids, it eventually leads to DEHYDRATION. This dehydration may be so severe that the resulting hemoconcentration induces an actual rise in the plasma chloride levels, in spite of a continuously negative chloride balance. Due to the "chloride shift" phenomenon the presence of *acid ketone-bodies* in the blood *may* cause the *passage of* chlorides from the plasma to the red cells, thus contributing to the decrease in plasma chlorides.



Pancreatic infantilism. 21-year-old man with diabetes mellitus, dwarfism and eunuchoidism. (Courtesy of Dr. E. H. Mason.)

Growth and Bone Structure. — The SKELETAL SYSTEM is not specifically affected by diabetes *mellitus* although, if the disease develops during childhood, the growth rate is sometimes greatly inhibited. In the rare cases of this so-called "pancreatic dwarfism" or infantilism," the impairment of skeletal development may also be partly due to interference *with the external secretion* of the pancreas and the resulting

increase in the other lipid fractions of the blood. A certain causal relationship may exist between *hypercholesterolemia* and the frequently observed diabetic arteriosclerosis.

Since much of the blood lipid circulates in the form of microscopic lipid particles, it is not surprising that the cells of the reticulo-endothelial system *tend to become loaded with lipids*. The accumulation of LIPID-CONTAINING HISTIOCYTES in the subcutaneous tissue, the spleen, etc., may give rise to xanthoma-like formations. (See: p. 524.)

LIPID INFILTRATIONS may also be seen in various tissues, such as the liver, the kidney and the heart. The frequent simultaneous occurrence of diabetes and adiposity has already been mentioned.

As in pancreatectomized animals, KETOSIS develops in spontaneous diabetes mellitus when the disturbance in carbohydrate metabolism becomes severe. Excessive quantities of "ketone bodies," namely acetone, acetoacetic *acid and β-hydroxybutyric acid appear* in the blood. Expressed as acetone, the normal ketonemia is about 1 5-2.5 mg./100 cc., in severe diabetic acidosis this may rise to 350 mg./100 cc or more. In clinical practice it is not customary, however, to determine the blood ketone level, *since ketonuria actually* precedes any significant degree of ketonemia and the former is generally a satisfactory index of the latter, although there is no absolute parallelism between the two. Since ketonuria is intimately related to acidosis, it constitutes an indication for prompt and rapid institution of therapy because it reveals an impending danger of coma.

Among the ketone bodies, acetone is the first to be demonstrable in the urine. It is followed by acetoacetic acid and finally by β-hydroxybutyric acid. The appearance of increasing amounts of the latter is a rough indication of the gravity of the intoxication, since in severe ketosis, it is in this form that most of the acids are eliminated. *Acetone is spontaneously formed* in solutions containing acetoacetic acid and probably represents a mere decomposition product of the latter, when it appears in blood or urine.

Normally the total daily urinary ketone body excretion (expressed as *β-hydroxybutyric acid*) is less than 1 gm. However, in unusually severe cases of acidosis the daily urinary ketone excretion may exceed 100 gm.

Nitrogen Metabolism. — Except for the increased tissue catabolism of untreated diabetics, the metabolism of protein and other nitrogenous products is not characteristically influenced by diabetes as such. The comparatively frequent association of renal lesions with diabetes may account for the occasionally observed ALBUMINURIA and HYPOPROTEINEMIA in such instances Hypoproteinemia, sometimes associated with edema, may also be due to injudicious dietary restrictions

There may be an increase in the N.P.N., especially in advanced diabetes and coma. This is also often the result of accompanying renal disturbances, dehydration, circulatory failure (decreased filtration pressure) or excessive protein catabolism.

Salt and Water Metabolism. — The POLYURIA of diabetics may be so severe that, in exceptional cases, the daily urine volume exceeds 25% of the total body weight. The specific gravity of the urine is usually high, however, because of the large quantities of glucose which are eliminated A specific gravity of over 1030 in a pale urine is rather significant, presumptive evidence of diabetes mellitus The total *daily urine volume and the specific* density of the urine tend to run parallel with the amount of glucose eliminated

Excessive diuresis is usually accompanied by some loss of TOTAL BASE, especially if the kidney's ability to pro-

GENERALIZED ARTERIOSCLEROSIS, especially atheromatosis and patchy thickening of the intima in the large vessels, is the most frequent vascular disease among diabetics; it may be at least partly due to hyperlipemia, arterial hypertension and obesity. Since the discovery of insulin, arteriosclerosis is increasingly more common among diabetics, because the specific treatment permits more of them to reach an age group at which such vascular diseases are prevalent. It is interesting that among diabetics, arteriosclerosis in the vessels of the heart and lower extremities is far more frequent than that of cerebral and renal vessels, although in non-diabetics the latter are more commonly involved

Other types of arteriosclerosis, especially the media calcification of Monckeberg, arteriolosclerosis and senile arteriosclerosis are less prevalent than atheromatosis of the large vessels

One of the most common and most dangerous complications of diabetes mellitus is the development of GANGRENE as a result of arteriosclerosis and of the consequent circulatory disturbances in the extremities. Any part of the body may be affected, but most commonly gangrene occurs in the lower extremities, especially the toes and heels. It is often preceded by a period of intermittent claudication.

If gangrene develops as a result of a comparatively slow arterial obstruction, so-called "wet necrosis" ensues, because *the circulation in the affected* part is insufficient to maintain normal tissue nutrition and resistance, but too *great to allow rapid mummification.* This type of gangrene provides an excellent medium for secondary bacterial *infection and brings* about the danger of septicemia Among diabetics it is much more common than the so-called "dry gangrene," which results from rapid occlusion of the arteries. The latter causes complete and immediate mummification of the affected area, with sharp demarcation from the normal tissue.



Diabetic gangrene. Note line of demarcation with commencement of granulation and healing The toe underwent almost entirely *spontaneous self-amputation*
(Courtesy of Dr E H Mason)







Calcification of arteries in diabetes. — A. B. and C. Female, age 58 years, had been diabetic for 8 years when these photographs were taken Pronounced calcification of posterior tibial, peroneal and dorsalis pedis arteries as revealed by X-ray of the leg
(Courtesy of Dr E H Mason)

impairment in calcium absorption. Quite frequently diabetic children, though underweight, are overgrown during the first few years of their illness. This may be due to excessive anterior-pituitary function.

Various types of "metabolic" ARTHRITIS are comparatively common in diabetics, but their pathogenesis is not understood.

Blood. — The blood count is usually normal, only rarely is there serious anemia in diabetics

Cardiovascular System. — CARDIAC DISEASE is perhaps the most common immediate cause of death among diabetics Statistical studies indicate that diseases of the coronary arteries are found in about 60% of all diabetics over 50 years of age, in contrast to less than 10% in non-diabetic patients Furthermore, among diabetics, women are almost as frequently affected as men, while in the general population, diseases of the coronary arteries occur five times more frequently in men Arteriosclerosis of the cardiac vessels may also explain the frequent occurrence of angina pectoris and myocardial infarcts among the diabetics.

Vascular lesions and gangrene occur most frequently in diabetics after the 40th year of age; uncleanliness, hypercholesterolemia, hyperglycemia, exposure to extremes of temperature, infections or irritating local injuries may act as predisposing factors. Males are slightly more frequently affected than females.

HYPERTENSION is a common accompaniment of diabetes mellitus and conversely, many hypertensive patients suffer, at least from a latent type of, diabetes characterized by decreased glucose tolerance. (See also: p. 524.)

Respiratory Organs. — The great predisposition of diabetics to respiratory infections, especially tuberculosis, has already been mentioned. With the progress of insulin therapy, however, the incidence of tuberculosis has decreased among diabetics. In untreated patients, the progress of both tuberculosis and diabetes is extremely rapid, since the two conditions tend to be mutually aggravating.

Muscles. — The muscular system is not specifically influenced by this disease but diabetics often suffer from easy fatigability, perhaps because of their low muscle glycogen reserves and the loss of muscle tissue resulting from excess protein catabolism. Peripheral neuritis may cause even more severe muscular disturbances (see below).

Nervous System. — In diabetic COMA the patient becomes increasingly more tired, loses his appetite and experiences great thirst, probably because of the dryness of the oral mucosa, consequent to dehydration. Subsequently drowsiness, nausea, vomiting, abdominal pain, air hunger (Kussmaul's breathing) and finally stupor with loss of consciousness result.

PERIPHERAL NEURITIS is very common, especially among diabetics of more than 35 years, who remained untreated because their comparatively mild metabolic disorder had not been recognized. Diabetic neuritis tends to become chronic and disabling, because of the accompanying pain along the affected nerves, the cramps, the paresthesias and sometimes even paralysis of the affected muscle groups. Thus involvement of the peroneal nerve may cause a "foot-drop." The tendon reflexes may disappear and trophic ulcers tend to develop. Often there is bilateral sciatica. Secondary nutritional disturbances probably play a part in the pathogenesis of these forms of neuritis. Peripheral neuritis is often accompanied by achlorhydria.

Some workers consider patchy degeneration of the nerve trunks, with thickening of the nerve vessels, as rather characteristic of diabetic neuritis. Adequate treatment of the underlying diabetes usually effects a fairly speedy recovery.

DIABETIC PSEUDOTABES is a very rare accompaniment of diabetes mellitus. It is characterized by the Argyll-Robertson sign (normal accommodation to distance but absence of pupillary response to light), absence of patellar reflexes, numbness of the feet, epigastric pain and urinary incontinence or retention.

Sense Organs. — DIABETIC RETINOPATHY manifests itself by small punctate hemorrhages, deep in the retina, near the macula. Sometimes there are also shiny or waxy punctate exudates, which coalesce to form large white patches. The condition occurs especially in middle-aged and elderly diabetics and eventually dims their vision.

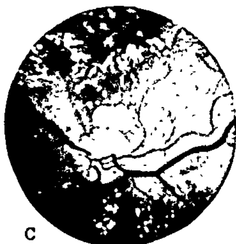
True DIABETIC CATARACTS are rare. They occur bilaterally and develop rapidly within a few days, most commonly in young, poorly-controlled patients. The lesion is characterized by subcapsular, vacuolar degeneration of the lens and tends to improve if the diabetes is adequately treated.

In addition to this type, in elderly diabetics senile cataracts occur with comparative frequency; these are not



Diabetic gangrene. — A. Gangrene in right foot (plantar view) prior to treatment — B. and C. Two stages of healing during a three month period of insulin treatment Note that even in this extremely severe case of gangrene, the foot was saved but for one toe which had to be amputated

(Courtesy of Dr E H Mason)



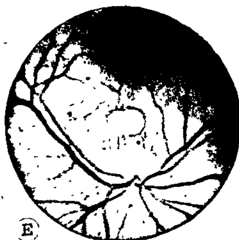


— C. Diabetic retinopathy with numerous "waxy" exudates, as seen with the ophthalmoscope.
— D. Diabetic retinopathy with "waxy" exudates and vitreous hemorrhage (black region in center)

is especially frequent in the genital region of women, owing to the irritating effect of urine rich in sugar. The itching is caused by the chemical irritation of the sugar itself, as well as by fungi, which find a particularly good medium in skin imbued with glucose-containing urine. Furuncles, carbuncles, erysipelas and trichophyton infections are often the result of the constant scratching due to pruritus.

XANTHOCHROMIA (XANTHOSIS) renders the skin yellowish in colour, especially in the palms of the hands, soles of the feet and the nasolabial folds. It is due to the accumulation of certain lipochromes, especially carotene, whose metabolism is disturbed in diabetes. This is often accompanied by xanthemia, resulting from an accumulation of lipochromes in the blood. It is merely of cosmetic significance, since it does not cause any functional disturbance. It largely depends upon the carotene intake.

XANTHELASMAS are fatty yellow tumors, which develop bilaterally around the inner canthus of the eyelids. They are not malignant but, if excised, they tend to recur. They are best controlled by an anti-diabetic treatment



— E. Normal retina, for comparison with C and D
(Courtesy of Department of Ophthalmology McGill University)

which maintains a normal blood-cholesterol level.

XANTHOMAS are small, usually symmetrical, cutaneous nodules about the knees, buttocks, forearms, elbows, the back of the hands, toes and neck. Their center is yellowish, their periphery reddish. They are the result of an untreated diabetic hyperlipemia. In some instances they occur on the tongue.

DIABETIC NECROBIOSIS LIPOIDICA manifests itself in the form of clearly de-



Ocular changes in diabetes mellitus. — A. Atrophy of iris pigment, one of the less important changes in diabetes — B. Normal iris pigment, for comparison with A. (Cont d)

responsive to treatment. Errors of refraction, paresis of accomodation, lipemia retinalis and wrinkling of the membrane of Descemet are also common. When the blood sugar of previously untreated diabetics suddenly drops (e g, from 300 to 100 mg %) under insulin treatment, the crystalline lens flattens (osmotic phenomena ?) and it may take up to 2 diopters to correct the blurred vision The lens becomes hazy and an incipient cataract may be suspected, but this defect regresses spontaneously

Digestive System. — The GASTROINTESTINAL TRACT is not characteristically influenced by diabetes as such, although impairment in the patient's general condition may secondarily cause gastrointestinal disturbances (e g, "diabetic diarrhea", achlorhydria).

The LIVER is often enlarged and infiltrated with fat. Hepatic cirrhosis is likewise not uncommon, but usually, function tests show the liver to be normal in diabetics. Cholecystitis and cholelithiasis are especially common among middle-aged, obese diabetics However, these diseases of the biliary passages are so frequently seen in obesity that their association with diabetes is not particularly characteristic

In bronze diabetes, there is rather extensive cirrhosis and hemosiderin infiltration in the hepatic stroma and liver cells; this is accompanied by marked cirrhosis and pigment deposition in other organs

Skin and Appendages. — FURUNCLES and CARBUNCLES, usually of staphylococcal origin, are common complications of diabetes, especially in overweight patients whose treatment has been neglected.

PRURITUS is perhaps the most common skin affection among diabetics. It

Diabetic GANGRENE is a severe complication, since it often necessitates the amputation of a limb and may be the cause of fatal septicemia. It is due to local nutritional disturbances consequent to vascular or nerve lesions which interfere with the maintenance of normal tissue metabolism and resistance The gangrenous tissue is an ideal medium for the proliferation of microorganisms and hence, predisposes to infection. The impairment of wound healing and decreased resistance to infection (due to the derangement in carbohydrate utilization ?) further aggravates the condition.

ARTERIOSCLEROSIS of the coronary vessels may be the cause of cardiac infarcts and attacks of angina pectoris Curiously, there is no close parallelism between the severity of the disturbance in carbohydrate metabolism and the intensity of the accompanying cardiovascular changes.

Various INTERCURRENT INFECTIOUS DISEASES, especially tuberculosis, may complicate the course of diabetes and are a comparatively common cause of death.

DIAGNOSIS

Physical Findings. — A definite diagnosis of diabetes mellitus cannot be made on the basis of the clinical manifestations alone. Yet a certain symptom complex is sufficiently characteristic to raise the suspicion of diabetes. It consists of general debility with ready fatigability, loss of weight in spite of excessive appetite, thirst accompanied by greatly increased diuresis, various types of pains, especially backache, itching of the skin (which in women, is most common around the vulva), in men, impotence and in women, disturbances of the sexual cycle

The looseness and fine wrinkling of the skin, accompanied by some pallor and dryness are also rather characteristic. In young patients and especially in women who take large amounts of insulin, the skin has a tendency to become waxy and transparent, while the wrinkles of the face disappear. This is sometimes described as the "insulin face." The common occurrence of other cutaneous manifestations, such as xanthoma diabeticorum, necrobiosis lipoidica diabetica, xanthelasma and xanthochromia have already been mentioned.

The great sensitivity to staphylococcus infections, furuncles, carbuncles, tuberculosis, as well as the high incidence of such degenerative changes as arteriosclerosis, diabetic retinitis, cataracts, gangrene, etc , have likewise been discussed.

Of course, many of these symptoms may be absent in proven diabetics and conversely, any of them may develop in patients who do not suffer from diabetes mellitus. Hence, more specific laboratory investigations are indispensable to verify the diagnosis

Laboratory Findings. — In frank diabetes, marked HYPERGLYCEMIA and GLYCOSURIA (persistent even during fasting), are most characteristic. The DECREASED GLUCOSE TOLERANCE (see : pp 513-515) yields especially valuable information in mild or latent cases, in which the fasting hyperglycemia and glycosuria are insignificant or absent.

KETONURIA, KETONEMIA, HYPERLIPEMIA and an increase in blood cholesterol, are all helpful additional indices, particularly in advanced cases. The detection of ketosis is of especial importance as a warning to institute immediate, active insulin therapy, in order to prevent the possible onset of coma.

Differential Diagnosis. — A number of conditions may give rise to glycosuria or hyperglycemia and it is important to differentiate these from true diabetes mellitus in order to select an appropriate therapeutic procedure

RENAL DIABETES is a condition in which glucose appears in the urine, although the blood sugar is normal or subnormal Because of its favorable prognosis, this condition has also been termed "diabetes innocens" or "benign



Xanthoma diabeticorum. Note typical xanthomatous excrescences on skin of arm
(Courtesy of Dr E H Mason)

marcated, reddish cutaneous papules, of a few mm. in diameter, which eventually may cause atrophy and exulceration of the skin It tends to occur most frequently in women whose diabetes has been neglected.

Mild HIRSUTISM may occur in untreated, young female patients, suffering from common diabetes mellitus and in this case it often yields to insulin therapy. Marked degrees of hirsutism are usually seen in the adreno-cortical or hypophyseal types of diabetes

Urinary System. — Proteinuria, lipid nephrosis and even various types of nephritis are not uncommon among diabetics. The most characteristic renal lesion, however, is the glycogen deposition in the convoluted tubules, which is almost pathognomonic of this disease. It is still doubtful whether the frequent association of hypertension and diabetes is secondary to such renal changes

The association of intercapillary glomerulosclerosis (often with degenerative changes in the arterioles and glomerular capillaries of the kidney) with nephrosis, hypertension and mild diabetes, is usually designated as the Kimmelstiel-Wilson syndrome.

Accessory Sex Organs. — In MEN, the most common sexual disturbance is impotence. It is often accompanied by loss of libido but when there is sexual intercourse, fertilization may occur.

In WOMEN, amenorrhea, early menopause and other menstrual disturbances are common. Libido and conceptions are decreased, abortions frequent. The fetuses of diabetic women are often oversized, with large livers, kidneys and spleens, sometimes there is erythroblastosis. The pathogenesis of this syndrome is not known

If diabetes appears before puberty, and remains untreated, the development of the sexual organs is delayed in *both sexes.*

Insulin therapy usually corrects all sexual anomalies except the impotence of the male and the habitual abortions in females

COMPLICATIONS

Most of the complications of diabetes have already been discussed under other headings Suffice it to enumerate them here briefly.

COMA is the most important complication of diabetes, since it is almost invariably fatal unless adequate therapy is rapidly instituted. It is characterized by the development of ketosis and acidosis, dehydration (thirst), gastrointestinal disturbances and progressive drowsiness with eventual complete loss of consciousness. The differences between diabetic and hyperinsulinemic coma will be discussed under "*Diagnosis*"

of ketone bodies due to depletion of liver glycogen.

Diabetic coma may also be confused with the unconsciousness subsequent to INTRACRANIAL HEMORRHAGE, especially since the latter is often accompanied by glycosuria (see above). The presence of blood in the cerebrospinal fluid obtained by lumbar puncture, the high intracranial pressure, the moistness of the skin and mucous membranes, the frequent occurrence of facial asymmetry, the sudden onset of *the condition, as well as the absence of* ketosis help to recognize the coma of cerebral apoplexy.

UREMIC COMA rarely gives rise to confusion with diabetic coma because of the patient's past history, the absence of *ketosis and hyperglycemia, the* cardiac enlargement and hypertension, as well as the many other characteristic manifestations of renal disease. The fact that the breath smells of urine in uremic coma and of acetone in diabetic coma, may also help to recognize the cause of the unconsciousness, although, perhaps too great an emphasis is sometimes laid upon diagnosis by the sense of smell.

PROGNOSIS

The prognosis of diabetes mellitus depends largely upon two factors:

(1) *The length of time elapsed between the onset of the disease and the initiation of treatment.*

(2) The intelligence and co-operative attitude of *the patient*

If adequate therapy is instituted soon after the onset of the disease, the remaining pancreatic tissue is apparently protected from the excessive strain of maintaining an abnormal carbohydrate metabolism Furthermore, degenerative changes in various organs especially in the cardiovascular system, have not sufficient time to develop Both these factors improve the prognosis.

The patient's co-operative and intelligent attitude is likewise of the utmost importance; spontaneous, complete recoveries are rare and the diabetic must learn to be largely independent, as regards his treatment, since, during the usually life-long course of therapy, he cannot always count upon the aid of a physician. The prognosis is very good if he learns to carefully control his diet and to check his glycosuria and ketonuria so that diet and insulin intake remain constantly balanced.

Statistical studies indicate that today, the life expectancy of diabetics, *even of those who contracted the disease in childhood, is almost as great as that of normal individuals.*

THERAPY

Prevention. — Since we now know that the disease is definitely inheritable, diabetics should not intermarry. Avoidance of overeating and performance of a certain amount of physical exercise are likewise valuable prophylactic aids, especially in presumably predisposed patients. The latter must also submit to periodic check-ups, by a competent physician, in order to recognize the disease as early as possible, should it develop.

Diet. — It is of the utmost importance that the adult diabetic maintain his weight 5 to 10 lbs. below the standard. The CALORIC REQUIREMENTS are best *expressed per Kg of the normal* standard weight, rather than in terms *of the actual weight of the patient.* 35 calories per Kg of standard weight *are recommended for the undernourish*ed and about 18 calories for the overweight diabetic patient In conjunction with other therapeutic measures, this will lead to a weight increase in the former and a loss of weight in the latter As the change in body weight progresses the caloric intake should be adjusted.

In the pre-insulin era, special emphasis was laid upon the relative intake of carbohydrate, fat and protein but now that, with the aid of the pancreatic

glycosuria." It is due to a lowering of the renal threshold for glucose elimination and is not related to any disturbance of insulin production. As previously stated, the normal threshold of sugar elimination is between 150 and 180 mg.%, but in renal diabetes it may be as low as 70 to 100 mg.%, while in true diabetes mellitus it is usually increased in cases of long standing, sometimes to as high a level as 250 mg.%. Comparative blood and urine sugar determinations, especially during glucose tolerance tests, permit the recognition of this condition.

"ALIMENTARY GLYCOSURIA" is always due to a lowered renal threshold for glucose. It is claimed that in some cases it may be the result of an increased absorption of sugar by the intestinal epithelium, but this has never been proven Prolonged *starvation* and *liver cirrhosis* may also cause glycosuria, following sugar ingestion, presumably due to a decreased ability to form glycogen.

INTRACRANIAL PRESSURE due to cerebral tumors, brain trauma or arterial hypertension, may give rise to glycosuria and hyperglycemia In these cases the detection of specific signs of intracranial pressure and the past history of the patient yield important differential diagnostic criteria (See also intracranial hemorrhage below.)

NEPHROSIS may decrease the renal sugar-threshold due to an impairment in the glucose-reabsorbing ability of the tubular epithelium. It is accompanied by other manifestations of nephrosis.

Metabolic disturbances, causing the URINARY ELIMINATION OF SUGARS OTHER THAN GLUCOSE, such as levulose, pentose, lactose or galactose, may be recognized by special analytic procedures which permit their chemical identification

During PREGNANCY the renal threshold may be sufficiently decreased to cause glycosuria. Lactosuria does not occur in pregnancy but is common during LACTATION.

HYPERTHYROIDISM is frequently accompanied by a decreased renal threshold for glucose, but may also be associated with true diabetes mellitus In some cases, though not invariably, treatment of the hyperthyroidism corrects the disturbance in carbohydrate metabolism.

Various types of HYPERPITUITARISM, especially acromegaly and Cushing's disease, are often accompanied by glycosuria and hyperglycemia. The same is true of the various HYPERPLASIAS AND TUMORS OF THE ADRENAL CORTEX which lead to an increased production of gluco-corticoids. The presence of other characteristic endocrine disturbances, usually permits the diagnosis of these diseases. The comparative insulin resistance of patients suffering from pituitary or adrenal diabetes may also be of differential diagnostic significance, although it is not sufficiently constant or specific to be regarded as pathognomonic.

HYPOGLYCEMIC COMA, due to islet cell adenomas or excessive insulin treatment, may bear a striking resemblance to diabetic coma. Failure to distinguish these conditions, particularly in patients known to be diabetic, has often led to fatal errors due to the administration of insulin to patients who already suffered from severe insulin intoxication. The dryness of the skin and mucous membranes, the hypotension of the eyeballs, glycosuria, hyperglycemia, the presence of acetone bodies in the urine and the diminution of the blood CO_2 are characteristic indices of diabetic coma. In insulin hypoglycemia the skin and mucous membranes are usually moist, the tonus of the eyeballs is normal and there are no signs of hyperglycemia, glycosuria, ketosis or acidosis. Yet, occasionally, severe insulin hypoglycemia leads to the appearance of minute amounts



Diabetic lipodystrophy. — A. and B. 32-year-old woman, who has been under treatment for diabetes during 9 years and developed marked fat tissue atrophy at the sites where she injected herself with protamine-zinc-insulin (buttocks, anterior surface of thighs) Condition has improved following change to crystalline insulin

(Courtesy of Dr E H Mason)

sulin, are preferable Even these should be administered only if it is impossible to keep the urine sugar-free by mere dietary measures It will be remembered that slowly-acting insulins tend to cause their maximum hypoglycemic effect many hours after injection, often during the prolonged fast of the night. This introduces the possibility of dangerous complications, hence it is usually best not to give more than 20 units of protamine-zinc-insulin per dose

The determination of the optimum dosage is largely a matter of experience.

As a general rule it is recommended to give half as many units of protamine-zinc-insulin as the number of gm. of glucose eliminated by the patient during 24 hours Thus a diabetic, who excretes 40 gm of glucose, should receive 20 units of insulin In each case, however, the dose should be adjusted to the individual requirements of the patient and it is customary to start with a single daily dose of 10-15 units of protamine-zinc-insulin, given 30 minutes before breakfast. This dose is raised by 5 to 10 units daily until glucose disappears from the urine. By determining the glucose content of the

hormone, the utilization of sugars can readily be normalized, the most important dietary factor is the total caloric intake; it governs the insulin requirement.

1 gm. of PROTEIN per Kg. of the standard (not the actual!) body weight is adequate to maintain a normal nitrogen equilibrium in the adult patient. It is important to remember, however, that children need additional protein in order to permit normal growth.

The CARBOHYDRATE intake should be kept as low as possible in mild diabetics whose condition may be controlled *without insulin. In severe diabetes,* however, where insulin must be administered anyway, the carbohydrate intake may be augmented in accordance with the dose of insulin given. In patients in whom it is believed that insulin will not be necessary, usually 100 to 120 gm. of carbohydrate are allowed to start with; this amount being raised up to 200 gm. per day if tolerated without alimentary glycosuria and hyperglycemia. If the total caloric value of the diet is low, even 250 gm. of carbohydrate may be adequately metabolized under the influence of but little insulin.

When the protein and carbohydrate quota is thus established, the amount of FAT to be allowed is given by the total caloric value permissible for the patient. This is readily computed, knowing how many calories are required (see above), and that protein provides 4, carbohydrates 4, and fat 9 calories per gm. Restriction of the fat intake below this level is necessary only in cases of severe diabetic hyperlipemia or xanthoma diabeticorum.

It is probable that diabetics require an even greater supply of VITAMINS than do normal persons. This appears to be especially true of the vitamin-B complex which seems to play an important rôle in carbohydrate metabolism.

As regards the DISTRIBUTION OF MEALS, it is recommended that the mild diabetic, who takes no insulin, should receive three approximately equal meals; the patient taking one dose of protamine-zinc-insulin per day, should receive 1/5 of the carbohydrates at breakfast, 2/5 at lunch and 2/5 late in the evening; patients receiving several doses of insulin should receive their meals in such a manner as to supply the maximum amount of exogenous sugar at the time when the hormone actions reach their peaks.

Several SPECIAL DIETS have been recommended *but for these, as well as* for the details of menu making, the reader must be referred to more specialized texts. Indeed, even these can only give general information because of the great individual variability in the metabolism, food predilections and occupational factors (e.g., exercise) among diabetics. Only extensive experience in a diabetic clinic will really teach the physician the art of adjusting the diet and the insulin requirement to the personal factors prevailing in each case.

Insulin. — In discussing insulin medication (see also . pages 485-486), it is important to keep in mind that in addition to the regular or unmodified insulin, the hormone is now available in combination with various agents which delay its absorption and thus regulate and prolong its activity. The effect of unmodified insulin is very rapid but transitory. This is a definite disadvantage in the routine treatment of diabetics. The brevity of action requires frequent injections throughout the day and the steepness of the resulting blood-sugar drops introduces a constant danger of severe hypoglycemic attacks unless sufficient sugar is continuously administered. For these reasons, in the routine treatment of diabetics, the modified, slowly-acting insulins, especially protamine-zinc-in-

meal and if it is found to be 150 mg.% or less, the control of the diabetic condition may be regarded as satisfactory. If it is above 150 mg.%, crystalline-zinc-insulin (starting with 8-12 units) is administered ½ hour before breakfast. This dose is raised until the blood sugar becomes normal 4 hours after the injection. At that time, the blood sugar one hour after the noon meal is again verified; if it is more than 150 mg %, crystalline-zinc-insulin must be administered before the noon meal also. If only one dose of protamine-zinc-insulin is given daily, adequacy of the control is checked by the highest blood sugar after the noon meal.

If crystalline-zinc-insulin is administered in two daily doses (before breakfast and before night meal), control is judged by the highest *fasting blood* sugar during the day

By using a planned system, such as that outlined above, diabetic patients are brought under control much more quickly and require less insulin than otherwise. With intelligent and co-operative patients, the period of standardization also suffices for instruction in the basic principles of self-treatment (control of diet, injection of insulin, recognition of complications, urine analysis, etc)

In the procedure *of standardization for children*, it is important to insure good nutrition permitting growth and weight-increase, in accordance with the theoretic mean for the actual height and age of the patient. With children much above average in height, a compromise has to be accepted, since otherwise, the caloric intake would be too high.

The diet is built up slowly to this objective starting with the same low values as in the adult (namely, protein 50 gm., fat 50 gm., carbohydrate 50 gm.) The recommended protein intake per Kg. of body-weight is 5 gm. between birth and 5 years, 4 gm. between 6 and 10, 3 gm. between 11 and 15 and 2 gm. between 16 and 20 years, in adults, 1 gm. of protein per Kg is considered adequate. It is also important to remember that *children* should always receive an adequate supply of milk and vitamins. Because of the great insulin-sensitivity of children, the dosage should be changed very gradually.

Diabetic Coma. — As soon as this condition is definitely recognized, it is recommended to give 50 units of crystalline INSULIN intravenously and 100 units subcutaneously. Additional subcutaneous doses of 10 to 20 units are subsequently administered, at 2 hour intervals, until the patient regains consciousness and glucose disappears from the urine. It is also advisable to determine the alkali reserve and continue treatment until it rises to 35-40 volumes % and qualitative tests for urinary ketones become negative.

INTRAVENOUS FLUID ADMINISTRATION is advantageous in any case, in order to combat the dehydration and if it is decided to give insulin without glucose, isotonic sodium-chloride should be infused intravenously in comparable doses, that is, one L. per 6 hours. *It is customary also* to administer 1-2 L. of isotonic sodium-chloride subcutaneously, or per rectum, during the same time interval. Because of the danger of aspiration pneumonia, *it is not advisable* to administer fluids by mouth during coma.

However, the restoration of the blood volume is of utmost importance; plasma transfusions may be necessary if saline fails to raise it.

In order to counteract the acidosis, some physicians recommend the administration of ALKALI (generally in the form of sodium lactate) in doses sufficient to raise the alkali reserve to about 35-40 volumes %. This, however, is not absolutely essential, since insulin, sugar and saline generally suffice to combat the acidosis.

During the treatment of diabetic coma, the patient may also require

urine four times a day, additional small doses of regular insulin, given before diurnal urine-sugar peaks, may suffice to maintain the patient sugar-free with doses smaller than those that would be required were only a single dose of protamine-zinc-insulin administered. In fact in general, combined treatment with regular and protamine-zinc-insulin, mixed in the same syringe, prove most efficacious.

Procedure of Standardization. — When beginning with the treatment of a neglected or hitherto untreated diabetic, it is well to follow a standardized plan. At the Royal Victoria Hospital (Montreal) the following *procedure of standardization for adults* has been used successfully, by *E. H. Mason*, during the last 16 years.

At the onset, the patient receives no insulin and is placed on a rigid diet for eleven days, according to the scheme outlined in the table below.

Day	Protein in gm	Fat in gm	Carbohydrate in gm
1	50	50	50
2	60	50	70
3	70	50	90
4	70	50	110
5	70	50	130
6	70	50	150
7	70	50	170
8	70	50	190
9	70	50	210
10	70	50	230
11	70	50	250

Most women are balanced on 70 gm., males on 80-100 gm. of protein per day, but the final amount should be adjusted according to age, weight and occupation in agreement with the principles discussed above.

The carbohydrate intake need not be raised above 200 gm., especially in obese patients, although, in males, up to 300 gm may be permitted, again adjusting the final level according to age, weight, occupation and possible complications, etc The total caloric intake should always be low and mainly covered by carbohydrate.

50 gm. of fat per day is generally sufficient throughout.

When the daily carbohydrate intake has been raised to 150 gm. (6th day of standardization), between-meal-feedings are started in the form of carbohydrate supplements 15 gm. in the forenoon, 15 gm. in the afternoon, 25 gm in the evening These additional meals need not necessarily consist of pure carbohydrates and it is also advisable to give milk, especially in the evening. The quantity of the three main meals is determined by subtracting the between-meal-feedings from the total quantity allowed, the balance being divided into three equal portions.

As soon as the blood sugar exceeds 150 mg.% one hour after breakfast, insulin administration is commenced in the form of protamine-zinc-insulin in doses of 12-16 units, ½ hour before breakfast This is progressively increased as the caloric intake is raised until the fasting blood-sugar becomes normal. After that, the blood sugar is determined one hour after the noon

meal and if it is found to be 150 mg % or less, the control of the diabetic condition may be regarded as satisfactory. If it is above 150 mg.%, crystalline-zinc-insulin (starting with 8-12 units) is administered ½ hour before breakfast. This dose is raised until the blood sugar becomes normal 4 hours after the injection. At that time, the blood sugar one hour after the noon meal is again verified; if it is more than 150 mg %, crystalline-zinc-insulin must be administered before the noon meal also If only one dose of protamine-zinc-insulin is given daily, adequacy of the control is checked by the highest blood sugar after the noon meal.

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CARDIAC STIMULANTS to prevent circulatory collapse, he should always be kept WARM since the thermoregulatory mechanism is severely deranged. If there is persistent vomiting and abdominal distension with pain, GASTRIC LAVAGE and ENEMAS are recommended. If the bladder becomes distended the patient can be CATHETERIZED. This may also become necessary in order to obtain urine specimens for analysis. In general, catheterization should be avoided, however, because in diabetics it often leads to infections, and eventual, spontaneous voiding is the rule if treatment is otherwise adequate.

In the treatment of diabetic coma it is well to follow a PREPARED ROUTINE, such as, for instance, that recommended by *Fowler* When the acidosis has reached the stage at which the patient is at least drowsy and has Kussmaul respiration, one proceeds as follows

(1) Crystalline insulin 100 units (intravenously) — injected from syringe into vein and not added to flask of fluid being administered

(2) Crystalline insulin 100 units (subcutaneously) — this is divided and 25 units injected in 4 sites in order to assure satisfactory absorption

(3) Protamine Zinc insulin 200 units (subcutaneously) — this is also divided and injected, 50 units in 4 sites

(4) Intravenous physiological saline 1000 cc followed by intravenous Ringer's solution in amounts sufficient to hydrate patient

(5) Gastric lavage — with 500 cc of warm physiological saline, left in stomach

(6) Penicillin intravenous and intramuscular

(7) Stimulants when indicated — usually caffein sodium benzoate gr viis (intravenously) — injection by syringe and not added to fluid administered intravenously

(8) Enema.

(9) Patient is given hot, well salted, fat-free broth (250 cc. q 1 h) as soon as swallowing is possible and five hours after administration of insulin, patient is given juice of two oranges with two teaspoons sugar q 1 h

These feedings will supply a significant amount of potassium and are continued for 12 to 24 hours.

Insulin Substitutes. — The use of drugs such as synthalin (decamethylenediguanidine) are contraindicated, since they depress the blood sugar simply by causing hepatic damage and thereby interfering with gluconeogenesis. While they thus may combat diabetes, the condition of the patient is actually aggravated.

Therapy of Complications. — Although it is not within the scope of this book to discuss the therapy of all the complications of diabetes, it is well to re-emphasize the importance of special care in the treatment of intercurrent infections, gangrene, etc., which tend to take a particularly severe course in diabetics, since all these complications aggravate the metabolic disturbance and are, in turn, adversely influenced by the latter It will also be recalled that almost any intercurrent derangement raises the insulin requirements.

SPONTANEOUS DIABETES MELLITUS IN ANIMALS

Spontaneous diabetes mellitus is comparatively rare in animals, although it has been described in certain species (e g., dog)

HYPERINSULINISM

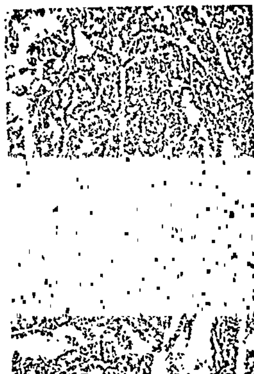
Terminology. — The term *glucopenia* is synonymous with hypoglycemia and should not be used to designate hyperinsulinism Hypoglycemia may, of course, be due to a variety of causes. — The term "*nesidioblastoma*" merely denotes tumors of the Langerhans islets irrespective of their ability to produce insulin.

DEFINITION

Hyperinsulinism is a condition in which the hormone production of the islets of Langerhans is sufficiently increased to produce detectable manifestations of overdosage

CLASSIFICATION

It is customary to subdivide the cases of hyperinsulinism according to the



Adenoma of Langerhans islets. Trabecular adenoma of Langerhans islets in a patient with hyperinsulinism
(Courtesy of Dr T Waugh)

nature of the causative pancreatic lesion into:

(1) *Overactive benign tumors* of the Langerhans islets (islet-cell adenomas or benign nesidioblastomas).

(2) *Overactive malignant tumors* of the Langerhans islets (islet-cell carcinomas or malignant nesidioblastomas).

(3) *Diffuse hyperplasia* of the Langerhans islets with increased hormone production. — This occurs, for instance, in the newborn infants of diabetic mothers

(4) *Purely functional* hyperinsulinism. Here it is claimed that the structurally normal islets respond, with excessive insulin production, to stimuli which would normally cause only a moderate insulin discharge. The existence of this last-mentioned type, however, has not been definitely proven.

PATHOLOGIC ANATOMY AND PATHOGENESIS

As previously stated, the pancreas in hyperinsulinism may merely reveal





Adenoma of the Langerhans islets. — A. 14-year-old boy who suffered from hyperinsulinism Note sharp delimitation of the (light) Langerhans islet adenoma from the darker pancreatic tissue, as viewed under low magnification In surrounding pancreas, a few (light) normal Langerhans islets are also visible — B. Higher magnification of the borderline between the normal pancreatic tissue (dark) and the Langerhans islet adenoma (light). The latter exhibits the trabecular type of arrangement
(Courtesy of Dr E H Mason)

diffuse hyperplasia and hypertrophy of the Langerhans islets, but usually there are adenomas or carcinomas of the islet cells. In the latter event, metastases may be found in distant organs, especially the liver.

The overdeveloped islet-tissue elaborates a great excess of insulin and most of the characteristic clinical manifestations are due to the resulting hypoglycemia. This is clearly evident from the dramatic therapeutic effect of glucose. Since the central nervous system depends almost entirely upon glucose as a source of energy, it is understandable that nervous manifestations play a prominent rôle in the syndrome.

Insulin hypoglycemia elicits a compensatory adrenaline-discharge which accounts for some otherwise inexplicable manifestations of hyperinsulinism (e.g., *spells of tachycardia, hypertension* and sweating).

INCIDENCE

Hyperinsulinism is a rare disease as judged by the fact that, up to the present time, only about 100 verified cases have been reported in the literature. It should be kept in mind, however, that the disease has only recently been discovered and hence, many cases may have escaped detection in the past.

As judged by the published data, there is no great predisposition to hyperinsulinism due to sex, age, heredity or climate.

CLINICAL COURSE AND COMPLICATIONS

The *clinical course of hyperinsulinism* is mainly characterized by nervous and gastrointestinal disturbances These tend to appear in spells, especially when the patient has been deprived of food for several hours (e g., *before* breakfast, undue delay of a meal), or under the influence of vigorous physical exercise and other factors conducive to hypoglycemia

At the time of the spells, the blood-sugar level is always less than 50 mg.%; often it is so low as to escape accurate determination.

Usually the disease develops rather gradually with mild attacks at first Only after several months or even years are the spells so severe as to cause loss of consciousness.

Apparently both the central and the vegetative nervous systems are affected. During the spells the characteristic manifestations are sweating, pallor or flushing of the skin, numbness of the lips, epigastric pain, hunger, nausea, chills, tremor, dizziness, great muscular weakness, cardiac palpitation and a rise in blood pressure. As stated above, many of these manifestations are obviously due to a compensatory discharge of adrenaline, which is known to occur under the influence of insulin hypoglycemia.

A fall in blood pressure is seen only in the terminal stages and represents an ominous sign as regards the prognosis.

Among the disturbances of the central nervous system, tonic or clonic muscular spasms and convulsions are the most characteristic. They are *usually preceded by restlessness*, inarticulate speech, diplopia and, in the absence of treatment, profound coma and death finally ensue.

During the attacks there are also characteristic psychologic disturbances such as spells of anger, negativism, difficulty of concentration, mania, lack of orientation and eventually unconsciousness. There is some resemblance between *these spells and alcoholic intoxication* Frequently, there is retrograde amnesia following the attack

The most frequent complications of hyperinsulinism are the results of traumatic injuries suffered during the convulsive attacks Metastases of overactive, malignant blastomas of the Langerhans islets may likewise complicate the clinical course

DIAGNOSIS

The following criteria are of value in establishing the diagnosis of hyperinsulinism :

(1) An abnormally low fasting blood-sugar level (below 60 mg.%).

(2) Attacks, with the above-mentioned clinical symptoms of hyperinsulinism, may be precipitated at will by withdrawal of food, while the administration of glucose causes *immediate* relief, simultaneously with the resulting *rise in blood sugar.*

(3) Glucose-tolerance tests reveal a subnormal initial fasting blood-sugar level and a blood-sugar peak not exceeding 120 mg.%. Restoration to subnormal values follows within two hours after glucose administration. Occasionally, however, there is a "diabetic" blood sugar curve, perhaps due to liver damage.

From the DIFFERENTIAL DIAGNOSTIC point of view, the following conditions should be kept in mind as other possible causes of hypoglycemic disturbances

(1) Addison's disease
(2) Simmonds' disease.
(3) Hypothyroidism
(4) Hepatic insufficiency (including v. Gierke's disease)
(5) Organic and functional diseases of the nervous system, especially epilepsy and anorexia nervosa
(6) Renal diabetes (Rarely accompanied by marked hypoglycemia)
(7) Progressive muscular dystrophy
(8) Excessive muscular exercise
(9) Various types of severe cachexia
(10) Lactation.

As a rule *it is not too difficult to eliminate confusion* with any of these conditions *on the basis of their specific* characteristics Should it be impossible, however, *to make a definite diagnosis*, exploratory laparotomy is indicated, especially *since the only effective cure* of hyperinsulinism is the surgical removal *of the excessive Langerhans* islet tissue and this may immediately follow, if necessary, during the laparotomy.

PROGNOSIS

In many instances, the progress of the disease is extremely slow and may extend over a number of years, but spontaneous cures have not been reported.

Following complete surgical removal of benign Langerhans islet tumors, the prognosis is excellent and even partial pancreatectomy for localized carcinomas of the islets may result in a permanent cure

THERAPY

The only rational therapy for severe *hyperinsulinism is the* SURGICAL *removal* of the causative excess Langerhans islet tissue

In mild cases, as a palliative measure, or if operation is impossible (because of extensive infiltration, metastases or refusal by the patient) the hypoglycemic effect of endogenous insulin is counteracted by supplying a constant intake of a DIET rich in protein and slowly absorbable carbohydrate. The patients should also always carry adequate amounts of sugar on their person, so that they may provide themselves with the necessary sugar in the event of an impending attack

During the hypoglycemic spells, about 5 gm of GLUCOSE solution, flavored with fruit-juice, should be administered every 10 minutes, if the patient is capable of taking nourishment Otherwise, 20 cc or more of a 50% glucose solution may be given *intravenously*, simultaneously with 20 gm of glucose or corn syrup dissolved in 250 cc of water, *per rectum.*

ADRENALINE injections (0 5 to 1 cc. *of the standard* 1 1,000 solution, subcutaneously) have been recommended, *because of their hyperglycemic action* and tonic effect upon the cardiovascular *system* However, *since the excess insulin* itself raises endogenous *adrenaline secretion, this measure is rarely, if* ever, necessary

TUMORS OF THE PANCREAS

The benign and malignant NEOPLASMS OF THE LANGERHANS' ISLETS have already been discussed in the chapter concerned with hyperinsulinism. *Suffice it to emphasize here that* very atypical carcinomas of the islets may not be conducive to any insulin overproduction and are then without endocrinologic significance.

The most common blastomas of the pancreas are the ADENOCARCINOMAS arising from the acinar or duct epithelium. These tumors develop most frequently in the sixth decade, although they may occur in younger patients.

The most common site for the occurrence of these cancers is the head of the pancreas, from which they gradually infiltrate into adjacent organs. Compression of the common bile duct tends to result in progressive jaundice, while *lymphatic metastases may eventually* invade a large part of the liver and stomach.

PROGNOSIS of these carcinomas is extremely grave, since they are generally not amenable either to surgical or to X-ray therapy. Only the tumors which arise in the tail of the pancreas are comparatively readily removable, but unfortunately, they do not tend to cause *detectable* symptoms until it is too late to remove them.

The pancreatic cancers which arise from the duct epithelium are usually composed of mucus-producing goblet cells with marked papillary hyperplasia. The excessive mucin production often makes it difficult to distinguish these pancreatic tumors from other cancers of the gastrointestinal tract, or those arising *in pseudomucinous ovarian* cysts

The acinar cancers are more readily recognizable, since they tend to imitate pancreatic tissue, although they are also very atypical.

Just as with other gastrointestinal tumors, pancreatic cancers may be par*enchymatous or scirrhous, the former* growing more rapidly than the latter.

MESENCHYMAL TUMORS of the pancreas are extremely rare, although sarcomas, fibromas, lipomas, etc, may develop from the pancreatic stroma.

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DUNCAN, G. G. *Hyperinsulinism*. Diseases of Metabolism, Chapter XIII, p 655, Ed by G G Duncan, W. B. Saunders Company, Philadelphia (1944).

A review (23 pages, 6 illustrations, 20 references), concerning the clinical aspects of hyperinsulinism.

DUNCAN, G. G.: *Diabetes Mellitus* Diseases of Metabolism, Chapter XVI, p. 700. Ed by G G Duncan, W. B. Saunders Company, Philadelphia (1944).

A systematic treatise (174 pages, 18 *illustrations, numerous tables and 155 references*), summarizing the clinical aspects of diabetes This excellent review is highly recommended to clinicians and students alike

DE DUVE, C.: *L'Action de l'Insuline* Ed. *Goemaere, Bruxelles (1945)*

A thesis (185 pages, 19 illustrations and a fairly large number of references), summarizing, mainly personal, experimental work on the mechanism of insulin action (In *French*)

FOSTER, N B.: *Diabetes Mellitus Designed for the Use of Practitioners of Medicine* J B Lippincott Company, Philadelphia (1915)

A monograph (243 pages, no illustrations very few references), outlining the management of diabetes during the pre-insulin era The volume is now merely of historic value

GRUBER-GOTTINGEN *Pathologie der Bauchspeicheldrüse* Handbuch der speziellen Pathologischen Anatomie und Histologie, Henke, F und O Lubarsch, *v/2*, 211, Verl von Julius Springer, Berlin (1929)

An extensive and extraordinarily well illustrated treatise, in which the pathologic anatomy of the pancreas is discussed with abundant references to the pertinent publications (In German)

JENSEN, H F *Insulin, its Chemistry and Physiology* The Commonwealth Fund, New York, Humphrey Milford, Oxford University Press, London (1938)

A monograph (243 pages, nearly 1 000 references, no illustrations), summarizing the chemistry and physiology of insulin The book acts mainly as a guide to the pertinent literature up to the date of its publication

JENSEN, H F *The Chemistry of Insulin* The Chemistry and Physiology of Hormones, p 69, pub Am A *Advancement of Sc*, Smithsonian Inst, Washington (1944)

A very brief synopsis (4 pages, no illustrations, no references) of facts concerning the chemistry of insulin

JENSEN, H F. *The Internal Secretion of the Pancreas* In The Hormones Pincus, G and K V Thimann (Ed) Academic Press Inc, Publ, New York (1948)

A review (31 pages, no figures 166 *references*) *summarizing the most important* facts concerning the chemistry of insulin and its mechanism of action

JOSLIN, E. P *The Treatment of Diabetes Mellitus* 6th Ed, Lea & Febiger, Philadelphia (1937).

A monograph (707 pages, very few illustrations, but a fairly extensive survey of the literature), dealing with the incidence, etiology, prophylaxis, physiology, pathology and therapy of diabetes Main emphasis is laid upon the clinical rather than the theoretic aspects The book is extraordinarily useful to all those engaged in the treatment of diabetes.

LAWRENCE, R D *The Diabetic Life. Its Control by Diet and Insulin* 13th Ed, The Blackiston Company, Philadelphia (1945)

A small-format booklet (223 pages, 18 illustrations, but very few references), whose main object is to bring the modern treatment of diabetes by diet and insulin within the scope of the practitioner It is a highly simplified, but most readable compendium, containing many helpful practical hints

ROOT, H F, AND C C BAILEY *Dietary Treatment of Diabetes Mellitus* Dietotherapy Clinical Application of Modern Nutrition, p 616, Ed by M G Wohl, W B Saunders Company, *Philadelphia (1945)*

A concise review (25 pages, no illustrations, 42 *references*), concerning the most important facts pertaining to the dietary treatment of diabetes

SOSKIN, S, AND R LEVINE *Carbohydrate Metabolism* University of Chicago Press, Chicago (1946)

An excellently written monograph (315 pages, 75 illustrations, more than 1 200 references) *intended to serve as a correlative* text for the teaching of carbohydrate metabolism to students of physiology and medicine A very clearly written survey of the biochemistry and energetics of carbohydrate *metabolism experimental* and clinical diabetes and the rôle of the endocrine glands in carbohydrate metabolism Despite its title, the volume also deals in some detail with certain aspects of protein and fat metabolism The book is highly recommended for those interested in the theoretic basis of metabolic disturbances

VI

THE PARATHYROIDS

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HISTORIC INTRODUCTION

In 1880, the Norwegian physician, Ivar Sandström, observed that within the thyroid tissue or attached to its surface, one regularly finds small, solid, epithelial organs, which differ from the thyroid mainly in that they contain no follicles. He gave them the name "parathyroids," but believed that they are *merely embryonic vestiges of thyroid* tissue. *A. Kohn* (1899), a histologist in Prague, first recognized that the glands are independent organs and gave them the name "epithelial bodies"

Since then, the parathyroids have definitely been proven to be important endocrine organs. In spite of their *extraordinarily small size, removal of* these glands is a fatal operation The chief purpose of the parathyroids is the regulation of calcium and phosphorus metabolism. In their absence, the blood calcium drops so markedly that violent hypocalcemic convulsions (tetany) ensue, while overdosage with parathyroid hormone causes removal of calcium and phosphorus from the bones, with concomitant bone destruc*tion in the form of a disease known as* osteitis fibrosa.

HYPOPARATHYROID tetany was first, rather vaguely, described by *Clarke* (1815) and *Kelie* (1816), in England, and then, in 1830-31, more precisely by *Steinheim and Dance*. In France, *Corvisart* (1852) designated the condition as "tetany." The Swiss surgeons, *Reverdin and Kocher* (1882), described postoperative tetany after *complete* thyroidectomy for goiter, without realizing that the condition was due to parathyroid deficiency. They referred to it as "tetania strumipriva" *Schiff* (1884) noted that in the cat and dog, complete thyroidectomy results in fatal tetany, while the rabbit shows no such manifestations. The reason for this species difference was not known at the time, but now we realize that *thyroidectomy causes no tetany in the* rabbit because, in this species, there are external parathyroids at some distance from the thyroid. Only in *1893*-1910, could *Gley,* in France, and *Vassale and Generali,* in Italy, demonstrate that removal of all parathyroids results in fatal tetany, even if the thyroid is *left intact. Thus, the* syndrome was recognized as due specifically to parathyroid insufficiency. This view was further supported by the *careful studies* of *Erdheim* (1901-14) in Vienna, who designated the condition as "tetania parathyreopriva," to distinguish it from clinically similar forms of tetany, due to other causes. Finally, in 1908, *MacCallum* and *Voegtlin*, in Baltimore, showed that parathyroid tetany is due to hypocalcemia, thereby supplying the last important fact for the contemporary interpretation of the disease.

The first active PARATHYROID EXTRACTS were prepared independently and almost simultaneously in the United States by *Hanson and Berman* and in Canada by *Collip* (1923-1926).

OSTEITIS FIBROSA has previously been confused with osteomalacia and osteitis deformans (Paget's disease). In 1891, however, *v. Recklinghausen* gave an excellent description of osteitis

fibrosa, clearly delimiting it from other bone lesions. The first parathyroid adenoma was described in 1900, by *Santi*, who did not suspect, as yet, that such tumors could cause bone destruction.

The cause of osteitis fibrosa had been surmized by *Askanazy* (1904) who, described a pertinent case in which there was in the thyroid a tumor, which he considered as possibly of parathyroid origin. Subsequently, the parathyroid theory of osteitis fibrosa was clearly formulated in 1915 by *Schlagenhaufer*, who even suggested that parathyroidectomy may be the logical therapy, although he had no occasion to try it. It was not until 1925 that, in Vienna, *Mandl* removed a parathyroid adenoma in a patient suffering from this disease and noted a remarkable improvement.

The final proof of the parathyroid etiology of osteitis fibrosa was given, in the United States, by the animal experiments of *Jaffe, Bodansky and Blau* (1930), who reproduced the characteristic bone lesions in animals, by overdosage with parathyroid hormone.

More recently, it has been found that experimental parathyroid hormone *overdosage may cause specific skin* lesions in animals (scleroderma) and that in the event of severe renal insufficiency, the glands produce an excessive amount of hormone in order to maintain normal blood calcium and phosphorus levels, in spite of the deficient urinary elimination. These observations strongly indicate that the scope of the parathyroids in physiology and internal medicine is much broader than has hitherto been suspected.

NORMAL MORPHOLOGY

ANATOMY

In man there are normally four yellowish-brown, ovoid or pear-shaped cated on the posterior ral thyroid lobes One parathyroids or para- ttached near the cranial inferior parathyroids or

ARTERY

ARTERY

RECURRENT LARYNGEAL NERVE

Anatomy of the parathyroids
(Redrawn after H Gray Anatomy of the Human Body Lea and Febiger, 1942)

parathyroid III) near the caudal pole of the thyroid lobes. The glands are usually embedded in the connective tissue capsule of the thyroid and only rarely within the thyroid itself. In any event the parathyroids have their own connective tissue capsule which separates them from the thyroid. Accessory parathyroids are quite common as we shall see in the section on Malformations. (See p 561.)

The size and position of these glands is rather variable but on the average, each parathyroid weighs 20-50 mg. and measures about 6 5 x 3.5 x 1.5 mm.

HISTOLOGY

Histologically, the parathyroids are composed of closely packed polyhedral epithelial cells, arranged in irregular clumps or cords. Between these there is a loose connective tissue stroma and a delicate framework of reticular fibres.

The EPITHELIAL CELLS are mainly of two types, the chief cells (also known as principal or chromophobe cells) and the oxyphil cells (or eosinophil cells). The *chief cells* are the most numerous. In children up to 7-10 years, as well as in most laboratory animals, they compose the entire parenchyme. Their cytoplasm is clear and free of granules, their nucleus vesicular and large. Occasionally, some chief cells arrange themselves to form small follicles containing colloid and imitating thyroid tissue.

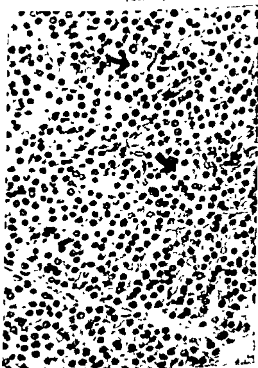
The *oxyphil cells* possess intensely acidophil cytoplasmic granules and are somewhat larger than the chief cells Their nucleus is comparatively small and dense They rarely participate in the formation of acini and resemble the eosinophil cells of the anterior-pituitary.

Several intermediate cell types have been described but these are of lesser importance. Both kinds of cells contain mitochondria, a Golgi net, glycogen and neutral fat granules.



Normal parathyroid (Man). Note massive arrangement of cell-cords in parathyroid, in sharp contrast with the follicular structure of the adjacent thyroid (upper part of the picture) As is very often the case in adults, fat cells are plentiful in the parathyroid stroma (Low magnification)

(Courtesy of Dr W Bonin)



Normal parathyroid (Man). Eosinophilic cells (arrow) are greyish and their nuclei are smaller than those of the clear chief-cells

The STROMA consists of connective tissue trabeculæ, which invade the gland from the capsule and contain the vessels and nerves. The fat cell content of the stroma, which is negligible in children, increases with advancing age.

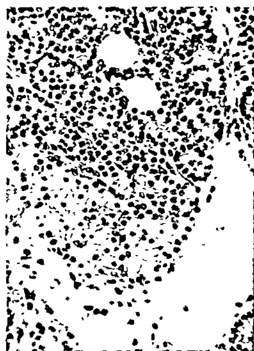
The ARTERIES enter the parathyroids at the hilus. The inferior parathyroids are supplied by branches of the inferior and the superior parathyroids, by branches of the superior thyroid arteries. Sometimes, both pairs of glands are supplied by branches of the inferior thyroid arteries or an anastomosis between the latter and the superior thyroid vessels. Knowledge of the vascular supply is of practical importance, since interference with the arteries during subtotal thyroidectomy may result in fatal tetany. Within the glands, the arteries break up into a fine network of sinusoids surrounded by reticular fibres; the latter are contiguous with the epithelial cells since there is no basement membrane. The principal VEIN of each parathyroid leaves the hilus to discharge its blood into the veins of the thyroid, trachea or esophagus.

The NERVES are mainly periarterial, unmyelinated, sympathetic fibres of the vasomotor type.

COMPARATIVE MORPHOLOGY

Although parathyroid-like structures have been reported in FISH, it is generally agreed that true parathyroids do not develop in animals lower than the AMPHIBIA. In most of the anura, urodeles and reptiles, two parathyroids are found on each side. In BIRDS, a single, large, sometimes bilobed parathyroid or two separate large glands are attached to the lower pole of the thyroids; it will be remembered, that, in aves, these are situated within the thoracic cavity. The comparatively large size of the parathyroids in birds, may be due to the great strain on calcium metabolism occasioned by the periodic formation of calcified eggshells.

Among the higher laboratory animals, the CAT has four parathyroids, one internal (inside the thyroid) and one external pair which are usually attached to the thyroid but may be situated at some distance from it, for instance in the thymus. In the DOG, there are usually four parathyroids; two on the surface of the thyroid and two smaller ones, deeply imbedded in its tissue. Even the external parathyroids are closely attached and adherent to the thyroid so that complete thyroidectomy results in tetany. Only about 5-6% of dogs possess aberrant parathyroids in atypical locations. In the GUINEA-PIG, each thyroid lobe usually contains an internal parathyroid, while a pair of external glands are located at some distance from the thyroid However, the position of both pairs, as well as the presence of accessory glands is



Normal parathyroid. Note clear chief-cells, eosinophilic cells and a few vesicles.
(Courtesy of Dr P Masson)

subject to great individual variations. In MONKEYS and APES, the position of the parathyroids as well as their structure (presence of acidophil cells) is reminiscent of the conditions found in man. In some breeds, however, numerous accessory, external parathyroids are noted. In the MOUSE and RAT, there are usually only two parathyroids which are visible in the form of light dots, one on each side, embedded just underneath the thyroid surface. Accessory parathyroids are quite common, however, in these small rodents and they may account for the frequent absence of tetany, following complete ablation of the thyroid. In the RABBIT, the external parathyroids are larger than the internal, ellipsoidal in shape and situated at some distance, caudad from the thyroid. These external parathyroids are sufficiently large to be detectable — with some experience — by the naked eye.

These comparative anatomic data are of practical importance, since the experimental endocrinologist must know the position of these glands if they are to be removed for extraction, the production of parathyroid deficiency or the study of possible structural changes.

EMBRYOLOGY

The four parathyroids of man develop as paired structures from the dorsal diverticula of the third and fourth pharyngeal pouches. They are correspondingly designated as parathyroids III and IV Parathyroids IV are present in all animal species, above the fishes They form the single pair of internal glands of the species enumerated above as having only two parathyroids. The development of the usually external parathyroids III is less constant throughout the animal kingdom.

It is noteworthy that parathyroids III tend to follow the thymus in its caudad migration during ontogenesis. Hence, in the adult, they are situated below, or caudad, to parathyroids IV and represent the inferior pair.

The parathyroids of man develop early in embryonic life, between the 3 mm. to 7 mm. stage. Throughout embryonic life only one type of cell, the chief cell, is visible.

THEORIES CONCERNING THE HISTOPHYSIOLOGY OF THE PARATHYROIDS

We have no histologic criteria which would permit us to follow the process of hormone secretion in the parathyroid cells. Various types of granules, including the eosinophil droplets of the oxyphil cells, have been regarded as the precursors of PARATHYROID HORMONE. It is difficult, however, to evaluate such observations as none have been made in conjunction with biochemical (blood or bone calcium) or physiologic (nervous irritability) observations which might give an indication of the amount of hormone produced at the time when a certain histologic picture is observed. *It must also be kept in* mind that oxyphil cells are absent in the parathyroids of most animal species and that adenomas of either oxyphil or chief cells may cause hyperparathyroidism in man. It is believed that the chief cells can be transformed into oxyphil cells and that the two morphologic types merely represent different stages of activity. This theory likewise lacks definite proof.

The GROWTH AND REGENERATION of the parathyroid cells occur mainly by way of mitosis. It has been claimed that the rather acidophil subcapsular zone of the parathyroid acts as a germinal layer, just as does the glomerulosa of the adrenal, and that growth and regeneration proceeds mainly from here.

Little is known concerning the REGULATION OF PARATHYROID DEVELOPMENT AND FUNCTION, except that it is not markedly affected by the anterior-hypo-

physis, since hypophysectomy causes no pronounced parathyroid atrophy and no functional manifestations of parathyroid deficiency. It is known, however, that severe derangements of calcium and phosphate metabolism (e.g., hyperphosphatemia caused by renal insufficiency or dietary measures) can induce a compensatory hypertrophy and hyperactivity of the parathyroids. Perhaps the cells of the gland are directly stimulated by the chemical composition (calcium content, pH, etc.) of the blood, but this has not been proven.

CHEMISTRY OF THE PARATHYROIDS

CHEMICAL COMPOSITION OF THE GLANDS

In view of the small size of the parathyroids and the difficulty of obtaining large quantities for chemical analysis, it is not surprising that most of our data concerning their chemical composition (presence of lipid, glycogen, ascorbic acid granules, etc.) have been obtained by means of histochemical technics and have revealed no very striking differences from the chemical composition of other endocrine glands. It is noteworthy, however, that the iodine content of the human parathyroid is estimated to average only about 0 005%, thus differing sharply from the adjacent thyroid.

CHEMISTRY OF THE PARATHYROID HORMONE

The usual method of preparation consists in extracting cattle parathyroids with aqueous hydrochloric acid and precipitating the hormone with trinitrophenol. The precipitate is subsequently extracted with acid acetone and alcohol; the active material is reprecipitated by the addition of excess acetone. The final precipitate is dissolved in water and is then ready for clinical use. Better yields are obtained, however, if the original extract is precipitated with $(NH_4)_2SO_4$ at pH 6 0 and then adsorbed to benzoic acid

The hormone has never been isolated, but it is almost certainly a simple protein Examination of the purest preparations shows that their ultraviolet absorption spectrum is similar to that of other simple proteins, electrodialysis gives no evidence of an associated active group, and the biologic activity is destroyed by pepsin There is chemical evidence that the potency depends upon the presence of free amino groups (ketene acetylation).

GENERAL PHARMACOLOGY OF THE PARATHYROID HORMONE

STANDARDIZATION

Analytic Methods. — There are no reliable chemical methods for the determination of the parathyroid hormone

Bioassay. — The biologic evaluation of parathyroid preparations may be based on several specific physiologic effects but the most generally accepted technic is that in which the hypercalcemic action of subcutaneous injections in the dog, is used as an indicator In this test, one U.S P. UNIT is defined as 1/100 of the amount necessary to raise the serum calcium of normal dogs by 1 mg %, within 16 to 18 hours after a subcutaneous injection. Because of the great individual variability of the results, the use of at least 10 dogs weighing 10-15 Kg is recommended Even this method is not very satisfactory, it is more accurate, however, than most other technics, e g., those based on the hypercalcemia induced by the hormone in the cat or rabbit and the ability to cause bone changes or

increased urinary calcium excretion in the rat.

MODE OF ADMINISTRATION

Parathyroid hormone extracts are effective only when given parenterally. Usually they are administered by the subcutaneous route, although if a particularly rapid effect is desired, the hormone may be given intravenously. Upon oral administration, even large doses are entirely ineffective since the hormone is apparently destroyed by the digestive enzymes of the alimentary tract. The commercially available sterile parathyroid extract preparations are marketed in vials containing 80 to 120 units per cc.

SENSITIZATION AND DESENSITIZATION

Chronic treatment with parathyroid hormone does not tend to cause any CUMULATIVE EFFECTS providing the individual injections are not too closely spaced.

On the other hand, in the course of protracted treatment, both animals and man may become resistant to the usual effects of parathyroid hormone. As we shall see in the section on Experimental Physiology (see pages 552-555), the osteoclastic bone absorption elicited by short term treatment, gradually gives way to osteoblastic bone formation so that there is not only desensitization but an actual INVERSION OF THE RESPONSE to the hormone. Correspondingly, the effects of parathyroid extracts upon calcium and phosphate metabolism are likewise changed or actually reversed with protracted treatment There is no evidence, however, of any true antihormone formation against parathyroid hormone or of any absolute acquired insensitivity since the organism continues to respond although in an abnormal (reversed) manner.

If, after prolonged parathyroid hormone administration, treatment is suddenly discontinued, hypocalcemia may result as a "WITHDRAWAL EFFECT."

THEORIES CONCERNING THE PARATHYROID HORMONE

Biogenesis. — There are no convincing data concerning the mechanism of parathyroid hormone formation in vivo.

The view that irradiated ergosterol is transformed into parathyroid hormone within these glands or causes them to produce their specific incretion, has not been substantiated.

Fate of Parathyroid Hormone in the Body. —Although some investigators believe they have found parathyroid hormone in the urine, there is no definite evidence that the hormone can be excreted in an active form. The liver, which is so important in the detoxification of steroid hormones, appears to play no significant part in the metabolism of parathyroid hormone, since partially hepatectomized animals are normally resistant to its effects.

Mechanism of Parathyroid Hormone Action. — ACCORDING TO EARLIER THEORIES the main function of the parathyroids is to detoxify certain metabolites (e g., guanidine derivatives or ammonia). This view has been abandoned, but the mechanism through which the parathyroid hormone exerts its diverse actions is still not fully understood.

Probably most but not all the actions of the hormone are secondary to its effect upon calcium and phosphorus metabolism Thus, as we shall see later, the manifestations of acute parathyroid tetany can be prevented, not only by the hormone itself, but also by calcium administration Furthermore, most of the manifestations of parathyroid hormone overdosage can be simulated by other conditions causing hypercalcemia and hypophosphatemia (e g., metastatic calcification of soft tissues, renal stone formation) Con-

sequently, the greatest attention has been given to the question : how does the parathyroid hormone affect calcium and phosphate metabolism ?

It has been claimed that the primary action of parathyroid hormone is to lower the RENAL THRESHOLD FOR PHOSPHATES *(Albright et al.)*. Following administration of excessive doses of parathyroid hormone, there is an almost immediate increase in the phosphate content of the urine accompanied by a decrease in blood phosphates and a rise in blood calcium. It has been assumed consequently, that the first effect of the hormone *is to decrease the* renal threshold for phosphates: this leads to a loss of blood phosphate which in turn calls for the mobilization of inorganic phosphates from bones. *Since in the bones the phosphates are* present as calcium salts, the discharge of calcium into the blood necessarily follows.

Although this theory appears quite *logical*, the following crucial experiments definitely eliminate the kidney as the primary site of parathyroid hormone action :

(1) Complete nephrectomy in the intact rat causes osteoclastic bone absorption due to stimulation of the animal's own *parathyroids. Following* parathyroidectomy no such bone lesions are produced by complete nephrectomy Apparently, in the nephrectomized animal, there is an excess production of endogenous parathyroid hormone (probably to counteract the uremic hyperphosphatemia) and in spite of the complete elimination of renal phosphate excretion, this endogenous hormone exerts its *normal action upon the* skeleton.

(2) If an excessive amount of parathyroid hormone is administered to completely nephrectomized rats (irrespective of whether the *animals'* own parathyroids are present or not), it causes a more pronounced and more rapid osteoclastic bone absorption than can be produced by nephrectomy alone. It follows that even in the complete absence of *renal phosphate elimination*, exogenous parathyroid hormone exerts its normal effect upon the skeleton.

In support of the renal threshold theory, some investigators emphasized *that in nephrectomized animals* parathyroid hormone causes no marked rise in blood calcium. It is true that the hypercalcemic effect of parathyroid hormone is very slight after nephrectomy, but it becomes quite marked if the parathyroids are removed simul*taneously* with the kidneys and thus, the otherwise pronounced, compensatory increase in parathyroid hormone production is prevented.

It must be remembered, furthermore, *that in the uremic animal, the blood* phosphate level is extremely high: this interferes with the action of most hypercalcemic agents, because it promotes the formation of insoluble calcium phosphates, which *precipitate from the blood* after the saturation point is reached.

The theory of CALCIUM X *(Greenwald and Gross)* is based on the assumption that parathyroid hormone enters into an actual chemical combination with calcium. Thus is formed a water soluble but non-ionized calcium compound, somewhat similar in its physico-chemical properties to calcium citrate. The formation of such a soluble compound was held responsible for the dissolution of calcium from the skeleton and the resulting hypercalcemia.

There are no data indicating, however, that parathyroid hormone can enter into a chemical combination with calcium, hence, the theory had to be modified. The injection of soluble phosphates into intact animals causes the formation of a water soluble calcium-phosphorus compound, which is non-ionized and rapidly eliminated through the urine It has been assumed

increased urinary calcium excretion in the rat.

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precede the development of detectable histologic bone lesions. It must be remembered, however, that functional stimulation often antedates microscopically visible changes and that, as shown above, the assumption that the action is solely mediated by the kidney has been definitely disproven.

The possibility has not been excluded, however, that the hormone acts directly both upon the kidney and the skeleton.

Different Kinds of Parathyroid Hormones. — There is no conclusive evidence to show that the parathyroids produce more than one hormone.

EXPERIMENTAL PHYSIOLOGY OF THE PARATHYROIDS

EXPLANTATION AND TRANSPLANTATION OF THE PARATHYROIDS

Parathyroid tissue can be cultured in vitro. It also lends itself very well *to autoplastic and, somewhat less well,* to homoioplastic transplantation. This latter property proved of practical significance in the many instances of accidental parathyroidectomies during operations for goiter, where the parathyroids have taken upon reimplantation into the host. Heteroplastic transplantation of parathyroid tissue gives *rather questionable results.*

TECHNIC OF PARATHYROIDECTOMY

The surgical removal of the parathyroids *causes no great difficulty once* the glands have been found. This is not always a simple matter, however, especially if they are deeply embedded in the thyroid or situated, at a great distance from the latter, in the connective tissue. Their prominent and constant arteries can serve as guides in locating abnormally situated parathyroids.

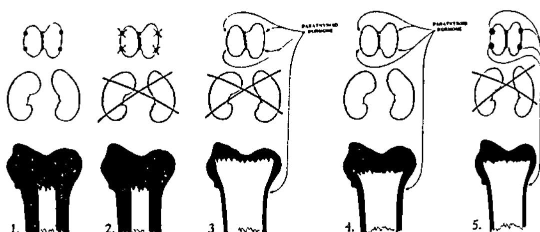
In the DOG and CAT even complete thyroidectomy almost invariably causes acute fatal tetany because the parathyroids are directly attached to the thyroid and hence, removed with the latter. It is possible, however, to selectively dissect the parathyroids from the thyroid or its capsule and thus to cause tetany without *any complicating* thyroid deficiency. In any case, the manifestations of thyroid deficiency develop so slowly that they are not detectable at the time the postoperative tetany appears.

In other species such as the HORSE, CATTLE, or RAT, postoperative parathyroid deficiency develops much more slowly, either because some ectopic parathyroid tissue is present in inaccessible locations (e.g., the thymus) or because the diet taken by these species is in itself less conducive to tetany than is that of the carnivora.

Technically, the removal of the *orthotopic parathyroids of the rat is* not difficult. The glands are readily identified as small, light grey nodules just below the capsule, near the upper pole or in the middle region of each thyroid lobe. They may be removed by dissection with a pair of fine pointed scissors or by thermocautery.

EFFECTS OF PARATHYROIDECTOMY AND PARATHYROID HORMONE TREATMENT

State. — Complete parathyroidectomy is always fatal, but the manifesta*tions of parathyroid deficiency differ* in the various species. It has already been mentioned that in the carnivora, of which the dog is the most commonly studied example, tetany is very acute. Two or three days after parathyroidectomy, the animal becomes indifferent to its surroundings and refuses food, then there is continuous vomiting, a premortal drop of body temperature, fibrillary twitches and later, more generalized spastic convulsions, with



Rôle of the kidney in the mechanism regulating parathyroid hormone action. — **1.** Intact control — **2.** Nephrectomized and parathyroidectomized — **3.** Nephrectomized and parathyroid hormone treated. — **4.** Parathyroid hormone treated. — **5.** Nephrectomized.

that parathyroid hormone — perhaps through some catalytic action — enhances the formation of such a "NEO-CALCIUM X." This assumption might explain the decreased calcium and phosphate elimination in hypoparathyroidism and the reverse condition in parathyroid hormone overdosage.

Even this modified theory fails to explain, however, why parathyroid hormone causes specific and characteristic histologic lesions in the bones (osteoclastic bone absorption under certain conditions, osteoblastic bone deposition under others), and how the formation of the hypothetic calcium-phosphorus compound, in hyperparathyroidism, results in the selective elimination of phosphorus through the kidney and of calcium through the intestines

The theory, which appears to be most readily compatible with all the pertinent observations, assumes that parathyroid hormone acts primarily upon the OSTEOBLASTS. As a purely vitalistic concept, this theory cannot claim to explain all the actions of the hormone in physico-chemical terms but it definitely singles out the bone as a primary point of attack. According to this theory, the parathyroid hormone, when given in large quantities, causes transformation of osteoblasts into osteoclasts and the latter — by virtue of their specific bone destroying properties — cause bone absorption with consequent discharge of skeletal minerals into the blood stream. Conversely, if small quantities of the hormone are given, or if the treatment is very prolonged, the osteoblasts are merely stimulated to proliferate. Hence, due to their specific bone depositing action, they increase the mineral content of the skeleton and cause the formation of "marble bones."

Only this theory attempts to account for the fact that not merely calcium and phosphorus but even the organic matrix of the bones is absorbed under the influence of excess parathyroid hormone and that, depending upon experimental conditions, this same hormonal principle can cause the osteogenic cells either to remove or to deposit bone In support of this concept, it has also been stated that even in vitro, parathyroid hormone causes osteoclast formation in bone explants Furthermore, parathyroids, unlike other tissues, cause local osteitis fibrosa when directly implanted into bone

Against the osteoblast theory it has been mentioned that the changes in calcium and phosphate metabolism — especially the phosphaturia — elicited by a parathyroid hormone injection,

calcium is ionized, only a negligible percentage being present in the form of some non-ionized organic complex (such as the hypothetical "calcium X"). It is customary in clinics to determine merely the total calcium content of the serum, since the ionized fraction can easily be calculated if the plasma protein concentration is known. The condition of the plasma calcium is of great physiologic importance since, for instance, depending upon the pH, protein and phosphate levels of the blood, a reduction of the blood calcium to about 4 mg % may or may not result in tetany. Conversely, primary changes in blood calcium concentration, can secondarily influence other plasma constituents, such as the phosphate concentration, since phosphates are not water soluble in the presence of excess calcium (formation of insoluble calcium phosphates). This must also be kept in mind in evaluating the relative importance of calcium and phosphates in the pathogenesis of parathyroid dysfunction. On the other hand under certain conditions (D-hypervitaminosis, bone tumors) hypercalcemia and hyperphosphatemia may coexist.

A number of other factors influence the blood calcium concentration; for example the calcium requirements of the skeleton, the pH, the relative proportion of calcium to phosphorus, and the presence of vitamin D in the food, all play a rôle in determining the absorption of calcium and phosphorus from the *intestinal tract*, its *deposition* in the body tissues and its concentration in the blood.

Parathyroidectomy causes a sharp fall in blood calcium to about 5 0 mg %, while treatment with large doses of *parathyroid hormone* raises it up to 18 0 mg.% or even higher. These variations are due to changes in the *physiologically active, ionized calcium* fraction. The sensitivity of the various animal species to the hypercalcemic effect of the hormone decreases in this order: man, dog, rabbit, rat, guinea-pig, fowl. Following chronic parathyroid hormone treatment there may develop an acquired resistance to this hypercalcemic effect both in animals and in man (see: p. 544). The principal factors influencing the concentration of serum calcium are expressed by the two equations:

$$\frac{(Ca^{++})\ (HCO_3^{-})\ (HPO_4^{---})}{(H^{+})} = K_1$$

$$\text{and}\quad \frac{(Ca^{++})\ (\text{Protein}^{--})}{(\text{Ca-protein})} = K_2$$

The BLOOD PHOSPHORUS is present partly in the form of acid soluble or inorganic phosphates and partly as organic phosphoric acid esters. The inorganic phosphates of the serum correspond to 2.5 to 3.5 mg.% in adults and 4.5 to 6 0 mg.% in children The organic phosphates can be hydrolyzed by *phosphatases, thus producing inorganic* phosphate. Almost all the inorganic *phosphate of the blood is present in* an ionized form and is ultrafiltrable. Changes in the calcemia may result in variations in the filtrability of the phosphates due to the formation of complex non-diffusible salts. This may be the case during the hypercalcemia caused by hyperparathyroidism.

Following *parathyroidectomy*, the inorganic phosphorus content of the blood rises up to 5.5 mg.% in the adult and *up to 7 0 mg % in the child. Conversely*, treatment with excessive doses of *parathyroid hormone* cause a marked decrease to about 2.0 mg.%. Following chronic parathyroid hormone treatment, both in animals and in man, an acquired resistance may develop to this hypophosphatemic effect of the hormone.

The *main calcium store* of the body is the SKELETON. About 2% of the adult organism is calcium and of this, approximately 99% is in the bones. These are composed of an organic ma-

extension of the hind limbs and marked retroflexion of the head. This may be accompanied by frothing at the mouth and protrusion of the tongue. Even between these sometimes epileptiform seizures, there is tachycardia, the gait is awkward and unsteady and the breathing is rapid and periodic. Finally, death ensues from asphyxia due to spasm of the laryngeal and thoracic muscles, respiratory paralysis or cardiac failure.

In the event of subtotal parathyroidectomy, a more chronic deficiency syndrome may occur, with anorexia, diarrhea, unsteady gait, slow movements and hyperexcitability of the muscles to electric stimulation. From this the animal can recover completely or a condition of latent tetany may develop in which the attacks alternate with periods of apparent well-being.

In the herbivora, or omnivora, parathyroidectomy causes a more chronic deficiency syndrome which, in the rat for instance, is characterized by defective calcification of the teeth, loss of hair, trophic disturbances in the nails, eczema, cataracts and finally, cachexia and emaciation. In this species, however, especially if the animal is adult, parathyroid deficiency is compatible with prolonged maintenance of life.

The survival after parathyroidectomy is greatly reduced if a low calcium high phosphorus diet is given (e g., meat) while high calcium low phosphorus rations improve the condition of hypoparathyroid animals (see also calcium and phosphate metabolism, below). Calciferol and other derivatives of vitamin D, which raise the blood calcium, are likewise beneficial. On the other hand, conditions which increase the calcium requirement, such as youth (calcium deposition in growing bones), pregnancy (calcium requirements of fetus) and lactation (calcium loss through milk) decrease resistance to parathyroidectomy.

Overdosage with large or frequently repeated doses of parathyroid hormone (sometimes seen in uncontrolled treatment of tetany in man) cause oliguria or anuria, loss of appetite, gastrointestinal erosions and hemorrhages, vomiting, drowsiness and ultimately death in coma. There is a general tendency for these signs to run parallel with the hypercalcemia and, in man, manifestations of severe overdosage are rarely detectable before the blood calcium reaches 14 mg.%. It is highly unlikely, however, that all manifestations can be ascribed to the hypercalcemia, since in osteitis fibrosa and after exogenous calcium administration, the calcemia may be equally high without there being such signs of overdosage.

Metabolism in General. — Neither parathyroidectomy nor overdosage with excessive doses of parathyroid hormone cause any prominent changes in BODY TEMPERATURE or the B.M.R., although fatal hypo- or hyperparathyroidism may be accompanied by a slight degree of hypothermia during severe crises.

Metabolism of Calcium and Phosphates. — Undoubtedly, the most important metabolic function of the parathyroids is their effect upon calcium and phosphate metabolism. In order to evaluate this profitably, it is essential to recall a few basic facts concerning normal calcium and phosphate metabolism

The normal human BLOOD CALCIUM ranges between 9.5-11 0 mg. per 100 cc. of plasma. The calcium content of the erythrocytes is negligibly small. Only about 50% of the plasma calcium is diffusible, the remainder is in combination with the serum proteins and hence non-diffusible through ultrafilters. In agreement with the law of mass action, the amount of calcium bound to proteins is dependent both upon the calcium and the protein content of the serum. Almost all the diffusible serum

calcium is ionized, only a negligible percentage being present in the form of some non-ionized organic complex (such as the hypothetical "calcium X") It is customary in clinics to determine merely the total calcium content of the serum, since the ionized fraction can easily be calculated if the plasma protein concentration is known. The condition of the plasma calcium is of great physiologic importance since, for instance, depending upon the pH, protein and phosphate levels of the blood, a reduction of the blood calcium to about 4 mg.% may or may not result in tetany. Conversely, primary changes in blood calcium concentration, can secondarily influence other plasma constituents, such as the phosphate concentration, since phosphates are not water soluble in the presence of excess calcium (formation of insoluble calcium phosphates). This must also be kept in mind in evaluating the relative importance of calcium and phosphates in the pathogenesis of parathyroid dysfunction. On the other hand under certain conditions (D-hypervitaminosis, bone tumors) hypercalcemia and hyperphosphatemia may coexist.

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trix, similar to collagenous connective tissue, in which inorganic salts are deposited. These salts, which are calcium phosphates and carbonates, represent about 50% of the total bone tissue so that the skeleton forms an enormous store of calcium, phosphates and carbonates. This mineral store is not a stable deposit: the organism can readily add to (bone deposition) or draw from (bone absorption) its skeletal minerals. The intimate physico-chemical mechanisms involved in bone deposition and absorption are not known as yet. It is certainly incorrect, however, to regard calcium deposition into bones as a mere process of precipitation, or its absorption from the bones as a simple phenomenon of dissolution. The phosphatases help to transform organic phosphorus compounds into inorganic phosphates, and vice versa, thus facilitating both deposition and absorption of bone

Histologic studies have shown, furthermore, that calcium may be withdrawn from the bones in three ways: (1) leaving the matrix intact (true decalcification), (2) by osteoclasts, together with the matrix (osteoclastic bone absorption) and (3) without osteoclasts but conjointly with the matrix (smooth absorption). Conversely, calcium may be deposited into a pre-existent, calcium-free osteoid matrix (calcification of osteoid) or it may be deposited together with excess matrix (new bone formation). [See . pp 552-555.]✓

Acute overdosage with *parathyroid hormone* depletes the skeleton of both calcium and phosphates (as well as the organic matrix) because of osteoclastic bone absorption. Conversely, chronic overdosage may increase the skeletal mineral deposits due to excess osteoblastic bone formation. This explains the often biphasic metabolic response to the hormone in which an initial hypercalcemia — due to liberation of bone calcium — gradually disappears or even gives way to hypocalcemia.

The lability of the bone salts is clearly demonstrated by experiments in which rats received radioactive-phosphorus until part of their bone phosphate was replaced by salts containing the radio-active phosphorus isotope. It was shown that within 20 days, 30% of this phosphorus is removed from the skeleton. It is also noteworthy that parathyroid hormone administration causes much more active bone absorption in areas where osteoclasts are readily formed (e.g., underneath the junction cartilages) than in other regions (e.g., the shafts). All this indicates that we can not yet explain the factors influencing bone deposition on the basis of simple physico-chemical phenomena

Parathyroidectomy causes much less obvious changes in skeletal structure and composition. (Usually only smooth absorption.)

In order to assess calcium and phosphate metabolism it is also important to consider the mechanism of their ABSORPTION and EXCRETION. The calcium ingested (in man 0 7-1 gm. per day) is mainly absorbed from the upper small intestine. The presence of excess phosphates (as in high phosphorus rickets), an increase in intestinal alkalinity (as in persistent vomiting), or excess fat (as in steatorrhea and celiac rickets) impede calcium absorption due to the formation of insoluble calcium phosphates or fatty acid soaps. Among the dietary phosphorus compounds "phytic acid" (inositol hexaphosphoric acid) especially abundant in cereals, is a particularly important rachitogenic agent, which interferes with calcium absorption by precipitation in the gut Vitamin D counteracts this effect of phytic acid and even causes much of its phosphorus to be absorbed and to become beneficial rather than harmful *(Mellanby)*. Conversely D-avitam-

inosis, due to inadequate intake or inadequate absorption of the vitamin itself (e.g., steatorrhea) likewise inhibits calcium assimilation.

In the normal human being, about 70-90% of the ingested calcium is eliminated in the feces, partly due to excretion through the lower intestinal tract, and partly because of incomplete absorption. The urine on the other hand contains very little calcium.

The daily phosphorus intake in man, is about 1.25 gm., much of which is derived from organic compounds from which intestinal phosphatase liberates readily absorbable phosphates. Unlike calcium, the phosphorus is excreted mainly (about 75% of the total) through the urine, as acid phosphate.

Parathyroidectomy decreases, while *overdosage with parathyroid hormone* increases, the urinary elimination of both calcium and phosphorus, sometimes up to a hundred times above normal.

The fecal excretion of calcium and phosphates is not significantly affected by parathyroidectomy in animals kept on a high-phosphorus low-calcium diet. On a diet rich in calcium and poor in phosphates, however, parathyroid deficiency induces a marked rise in the fecal elimination of both calcium and phosphorus. Consequently, on this latter diet, parathyroidectomy results in no marked phosphate retention since less phosphate is taken in and more is excreted with the calcium which binds the phosphates as insoluble calcium salts.

Metabolism of Magnesium. — The metabolism of magnesium resembles that of calcium Normally, about 50-80% of this element is excreted through the intestine and the remainder through the kidneys Parathyroid hormone slightly and temporarily increases the urinary elimination of magnesium, while parathyroidectomy tends to diminish it Occasionally, there is also a transitory increase in serum magnesium, following injection of parathyroid hormone. Although all these changes are inconstant, it is tempting to assume that there is some connection between magnesium and parathyroid hormone since phosphatase activity is dependent upon magnesium and chronic magnesium deprivation may cause a form of tetany without any disturbance in calcium or phosphorus metabolism. In clinical medicine, the highest and most consistently elevated serum magnesium values are found in chronic glomerulonephritis but the underlying mechanism is not clear.

Other Metabolites. — It is of clinical importance that parathyroid hormone may suddenly liberate large amounts of LEAD or RADIUM from the bones of patients who suffer from chronic intoxication with these elements. Just as calcium, these metals are stored in the skeleton and consequently they are released following bone absorption. This may elicit manifestations of acute intoxication and hence it is hardly desirable to use parathyroid hormone, e.g., for the "de-leading" of patients suffering from chronic lead poisoning. The *metal is deposited in the skeleton, specifically to avoid its acute toxic effects and it is preferable to let nature gradually liberate it from the bones in subtoxic amounts*

It is still doubtful whether parathyroid hormone has any specific effect upon WATER METABOLISM The diuresis which it produces may merely be a consequence of the deranged electrolyte metabolism and the renal damage occasioned by excessive amounts of the hormone

After parathyroidectomy, the PHOSPHOCREATINE (phosphagen) content of the muscles is diminished and the resynthesis, following muscular effort, of creatine and phosphoric acid into phosphocreatine is delayed. The increased chronaxia of parathyroidectomized ani-

mals may be related to this phenomenon since, within limits, the latter is inversely proportional to the muscle phosphocreatine content. This may partly explain the motor disturbances of parathyroid insufficiency.

PHOSPHATASES are enzymes which hydrolyze a variety of monophosphoric acid esters. Their activity is measured in units based upon their ability to liberate inorganic phosphates from organic monophosphoric esters, under standard conditions, in vitro. By definition, the phosphatase concentration in 100 cc. of plasma is calculated as the basis of the determination so that it is not customary to designate these as "units per 100 cc." but merely as units Four *types of phosphatases* are of biologic importance :

(1) Alkaline phosphatase with optimum activity at pH *9.3* (present in blood plasma or serum, bone, kidney, intestine, mammary gland, spleen, lung, leucocytes, adrenal cortex and testis).
(2) Acid phosphatase with optimum activity at pH 6 (present in erythrocytes and yeast).
(3) Acid phosphatase with optimum activity at pH 5 (present in prostatic epithelium, spleen, kidney, blood plasma, liver, pancreas)
(4) Acid phosphatase with optimum activity at about pH 3-4 (obtained from Taka diastase).

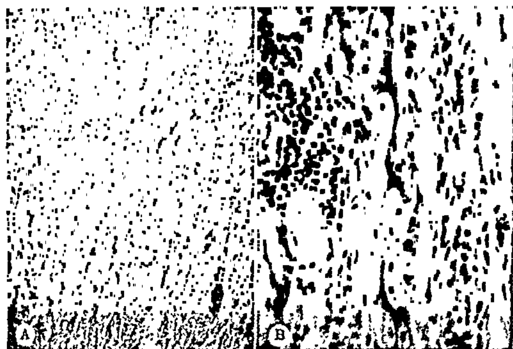
Significant variations in serum *acid phosphatase* have only been observed in metastasizing carcinomas of the prostate.

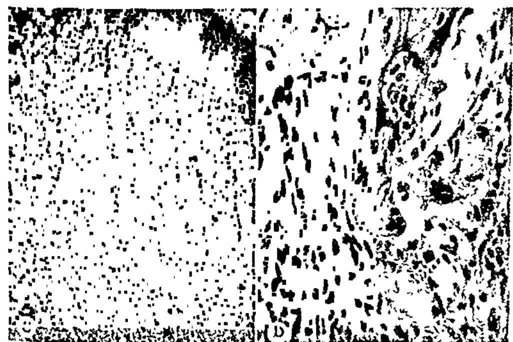
The *alkaline phosphatase* activity of the serum is significantly increased in parathyroid hormone overdosage but shows less consistent variations following parathyroidectomy. Since bone tumors likewise cause a marked rise in the alkaline phosphatase of the serum, it is probable that most of the serum phosphatase comes from the bones and that its rise is merely an accompaniment of bone reconstruction, rather than a specific effect of the parathyroid hormone. Apparently osteoblasts secrete phosphatase, which by hydrolyzing the salts of phosphoric esters brought to the ossifying zone in the bones, can cause an increased local concentration of phosphate ions and thus facilitates calcium precipitation. The enzyme also helps in the renal elimination of phosphorus, when the latter is liberated in excessive quantities from bone. Because of these multiple functions of the enzyme, an increase in serum phosphatase is not of great diagnostic importance, although the absence of a change in blood phosphatase speaks strongly against parathyroid hormone overdosage.

It must be remembered that increased *phosphatase values are greatly dependent* upon increased activation of the enzyme by other blood constituents (e g., magnesium, iron, manganese) hence, it is preferable to speak of the "phosphatase activity" rather than of the "phosphatase content" of serum.

Growth and Bone Structure. — Following *parathyroidectomy,* distinct and characteristic changes develop in the skeleton only if the course of the insufficiency is chronic. Thus, in young dogs, subtotal parathyroidectomy, and in young rats, complete removal of the orthotopic parathyroids, cause dwarfism due to a pronounced inhibition of skeletal growth. Histologically, we find irregularities along the lines of endochondral ossification of the long bones with the inclusion of cartilage islands among the trabeculæ in the subepiphyseal zone of the shaft. The picture is somewhat reminiscent of rickets, especially since the calcification of the osteoid is also defective.

In adults the skeletal lesions are less characteristic but the healing of bone fractures is always delayed in hypoparathyroid animals.

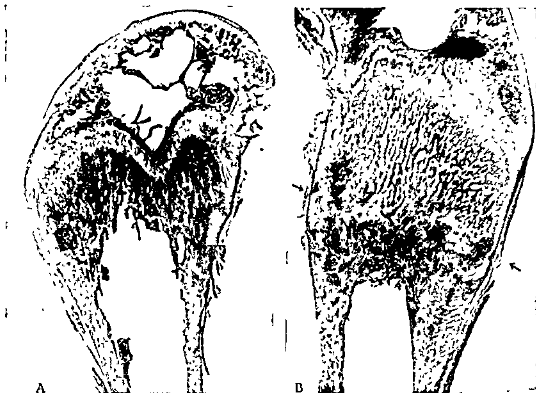




Effect of parathyroid hormone upon bones. — A. Tibia of a normal young rat Note epiphyseal cartilage (above) and regular trabecular pattern (low magnification) — B. Higher magnifica-

[illegible]

— D. High magnification of a region from the tibia of the animal shown in Fig C. Note proliferation of fibroblasts and numerous polynuclear osteoclasts in the process of lacunar bone absorption *The lesion is similar to that seen in spontaneous osteitis fibrosa in man.*

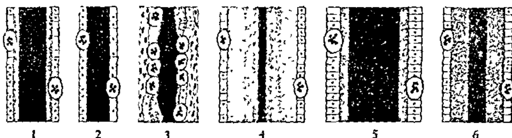


Effect of prolonged parathyroid hormone treatment upon the bones. — A. Longitudinal section through the lower extremity of the femur of a normal control rat Note regularity of epiphyseal junction cartilage and moderate development of diaphyseal trabeculæ — **B.** Cross-section through the femur of a similar rat chronically treated with parathyroid hormone Note increased density of the bone especially that part of the diaphysis underneath the growth-cartilage which was formed during the parathyroid hormone treatment. The approximate location of the junction cartilage at the commencement of treatment is still visible in the form of an irregular transverse line (indicated by arrows)

(After H Selye Endocrinology *16* 547 1932)

Overdosage with *parathyroid hormone* causes an excessive formation of osteoclasts, probably through the fusion of several neighbouring osteoblasts. This osteoclast formation is accompanied by lacunar bone absorption, which so weakens the skeleton that spontaneous fractures ensue. In young animals, the osteoclastic bone absorption is most intense in the subepiphyseal regions of the long bones and may result in the spontaneous detachment of the epiphysis from the shaft

Very small doses of parathyroid hormone or large (but sublethal) doses given for a long time — cause an inverse response with excessive proliferation of active osteoblasts These deposit excessive amounts of bone, thus imitating the clinical picture of "marble bone disease" or Albers-Schonberg's disease. As has been mentioned above, this reversal of the hormone effect upon the bones is accompanied by a corresponding inversion of its action upon calcium and phosphate metabolism. We are manifestly dealing with a bi-phasic reaction but the nature of this adaptation, or reversal of effect, is still unknown. It is not due to antihormone formation against the parathyroid hormone, minute doses of the latter cause osteoblast formation and bone deposition from the onset, without any initial phase of osteoclastic bone absorption and there is no actual loss of sensitivity to the hormone but merely a change in the type of response to it. It is tempting to assume that, depending upon the dosage, parathyroid hormone

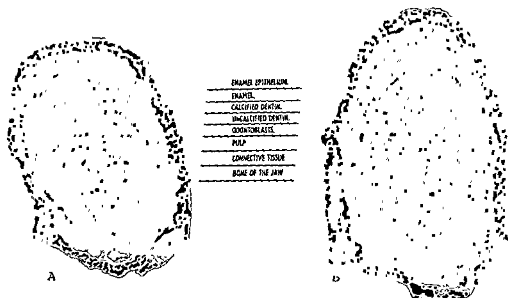


Various types of bone absorption and bone formation. — 1. Normal bone — 2. Smooth absorption (e g, hyperthyroidism). — 3. Osteoclastic absorption (e g, osteitis fibrosa) — 4. Decalcification or "halisteresis" Occurrence doubtful (e g, osteomalacia?). — 5. Excessive osteogenesis (e g, "marble bones"). — 6. Subnormal calcification of osteoid (e g, rickets).

can influence bone formation both in the positive and in the negative sense. This would help to understand why parathyroidectomy causes but mild skeletal changes which cannot be regarded as the counterpart of those produced by parathyroid hormone overdosage.

The TEETH show particularly characteristic lesions following parathyroidectomy. This is especially true of the incisors of rodents, which grow continuously throughout life. Thus, Erdheim noted that in the parathyroidectomized rat, the newly-formed dentin fails to calcify and the enamel is hypoplastic and irregular. The lack of dentin calcification is so characteristic of parathyroid insufficiency that it has even been employed as an indicator in the bioassay of parathyroid hormone. If a parathyroidectomized rat is repeatedly treated, at short intervals, with small doses of parathyroid hormone, rings of calcification appear within the otherwise uncalcified dentin, corresponding to each period of treatment.

Blood. — After prolonged parathyroid hormone treatment, multiple throm-



Changes in the incisors of rodents induced by parathyroidectomy. — A. Cross-section through a lower incisor of a normal rat Compare with Fig B — B. Cross-section through the lower incisor of a parathyroidectomized rat Note hypoplasia of the enamel and deficient calcification of the dentin Such teeth tend to be brittle with opaque and often depressed surface areas due to the enamel defect Parathyroid hormone rapidly restores this deficiency to normal

(Schematized after Biedl Innere Sekretion — Urban und Schwarzenberg Vienna 1922)



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Production of "Experi
symmetric arrangemen
to the eyes on both si
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(After H Selye Virchow's Archiv f path Anat 286 91 1932)

The occurrence of CATARACTS is frequently noted, especially in chronic parathyroid insufficiency, both in animals and in man.

Other Organs. — Neither parathyroid deficiency nor overdosage cause especially characteristic lesions in other organs except the METASTATIC CALCIFICATION of soft tissues, which is a common result of parathyroid hormone overdosage. The metastatic calcium deposits are most frequently in the kidneys (sometimes also calcified casts and renal calculi), heart muscle and intestinal walls, where they are macroscopically detectable in the form of irregular white spots.

In young rats, overdosage with parathyroid hormone may cause a skin disease resembling SCLERODERMA. This begins with an acute stage of edema and necrosis of the derma, later followed by calcification.

Conditions. — As previously stated, parathyroidectomy leads to particularly acute and severe manifestations of insufficiency in pregnant and lactating rats, probably because of their increased calcium requirements.

If pregnant or lactating rats are overdosed with parathyroid extracts, the skeleton of the offspring may also show defective development

PARATHYROID HORMONE CONTENT OF BODY FLUIDS AND TISSUES

In view of the comparative inaccuracy and insensitivity of the bioassay methods for parathyroid hormone, comparatively little is known about the metabolism of this principle Data concerning the normal and abnormal para-

bi have occasionally been observed because of a promotion of blood coagulation by the hypercalcemia. The blood count is not characteristically influenced by the hormone.

Muscles. — The most prominent manifestation of experimental parathyroid insufficiency is tetany. This is characterized by fibrillar twitchings of the muscles, followed by tonic (persistent) or clonic (jerking) muscular contractions with attacks of spastic retroflexion of the head. The latter phenomenon is due to contraction of the long muscles along the spinal column. Sometimes parathyroidectomized dogs and cats exhibit automatic, rhythmic movements as if they were swimming with their fore-limbs. In other instances, the movements are jerky and look as though the animal were shaking water off its skin.

There is increased excitability of the muscles by the galvanic current. A cathodal opening contraction, which normally would require 6 milliamperes (with the electrode placed upon the skin directly over the nerve), occurs in the tetanic animal with less than one milliampere.

The "time constant of accommodation" is also increased, that is, slow rates of change, in the strength of a stimulating electric current, suffice to produce excitation. With very low blood calcium values, the phenomenon of "neuro-muscular accommodation" may be entirely lacking.

The characteristic tetanic convulsions persist after section of the upper thoracic spinal cord, which means that supraspinal centers are not involved in their pathogenesis. On the other hand, the integrity of the spinal reflex arc is indispensable, since the convulsions are abolished by curare or section of the dorsal roots. Unlike the tonic and clonic convulsions, the fibrillar movements appear to be peripherally conditioned, since they persist for at least one day after section of both afferent and efferent nerves.

Characteristic morphologic changes in the muscles have not been observed in tetanic animals and parathyroid hormone overdosage causes no typical muscular lesions, other than the metastatic calcifications, which are also seen in other organs.

Nervous System and Sense Organs. — The possible rôle of the nervous system in the production of the tetanic motor disturbances has not been fully clarified as yet. However, as we have seen above, the major factor is a neuro-muscular disturbance although an increase and great instability of the chronaxia are also rather characteristic.

Parathyroidectomized animals have a special predilection for calcium and a decreased appetite for phosphates, so that they voluntarily choose a particularly suitable diet.



"Metastatic calcification" in the kidney of a rat treated with parathyroid hormone. This animal received 300 U S P units of parathyroid hormone in repeated, subcutaneous doses during 48 hours Note the calcification of convoluted tubules (black), as revealed in this section by a specific stain for c [illegible]

nature of this follicle formation remains mysterious.

It has been claimed that removal of the CAROTID BODY causes parathyroid enlargement in the cat, dog and rabbit. It will be recalled, in this connection, that in certain species (bird) there are close anatomic relations between the carotid gland and the parathyroids, both being located in the bifurcation of the common carotid artery.

Ablation of OTHER ENDOCRINE GLANDS causes no significant changes in the parathyroids.

Partial or complete NEPHRECTOMY results in hypertrophy and hyperplasia of the parathyroids, which, as previously mentioned, is apparently accompanied by increased parathyroid hormone secretion. This probably represents an effort to counteract, with an excess of parathyroid hormone, the hyperphosphatemia induced by renal insufficiency.

Hormones. — It has been claimed repeatedly that certain PITUITARY EXTRACTS stimulate the parathyroids to hypertrophy. This was ascribed to their content in a hypothetic "parathyrotrophic hormone." The relevant experiments are inconclusive, however, and the above-mentioned absence of any functional or morphologic manifestations of parathyroid failure following hypophysectomy, mitigates against the existence of such a pituitary principle.

The mild hypertrophy of the parathyroids in animals treated with FOLLICULOID HORMONES has been held responsible for the ability of the latter to influence bone formation and cause [illegible] somewhat doubtful.

PARATHYROID HORMONE overdosage, especially if long continued, may cause compensatory atrophy of the parathyroids.

Diseases. — The parathyroid changes characteristic of spontaneous HYPO- AND HYPERPARATHYROIDISM will be discussed in the chapters devoted to these diseases.

In congenital MYXEDEMA, due to complete aplasia of the thyroid, the parathyroids may be normal but occasionally they contain cysts and follicles such as are sometimes also seen in the parathyroids of goiter-bearing patients. These changes have been interpreted as indications of some functional relationship between the thyroid and the parathyroids, but there is little evidence to support this view. It is possible that in these cases the formation of cystlets is merely due to an interference with the nutrition of the glands which is received through branches of the thyroid vessels.

In ACROMEGALY there may be hyperplasia or even adenoma formation in the parathyroids. These changes are not sufficiently constant, however, to prove the existence of parathyrotrophic hormone.

Many bone diseases are accompanied by enlargement of the parathyroids. This is frequently the case in OSTEOMALACIA, RICKETS and metastatic CARCINOMATOSIS OF THE SKELETON. The parathyroid enlargement in patients with such bone diseases is secondary and due to the increased stress upon calcium and phosphorus metabolism, occasioned by widespread skeletal lesions

In MARBLE BONE DISEASE there may be a parathyroid adenoma but this has rarely been noted, perhaps because so few pertinent cases have been examined for it. As stated above, there is some experimental evidence suggesting that chronic parathyroid hormone overdosage may cause the formation of "marble bones."

In PAGET'S DISEASE (osteitis deformans) the parathyroids are usually normal.

thyroid hormone content of body fluids and tissues, as estimated by direct bioassay, will not be discussed here, since, in our opinion, they all require confirmation. The only definitely established pertinent fact is that the PARATHYROID ADENOMAS of patients with osteitis fibrosa have been proven to contain large amounts of parathyroid hormone.

Indirect evidence gives us much more convincing information. Thus, the *development of latent tetany following* PARTIAL PARATHYROIDECTOMY, indicates that a subnormal amount of parathyroid hormone is produced if only small remnants of parathyroid tissue are left in the body.

After HYPOPHYSECTOMY, tetany does not occur, even in so sensitive an animal as the dog, but subsequent parathyroidectomy in a hypophysectomized dog is immediately followed by fatal tetanic convulsions. This indicates that the hormone production of the parathyroid is not significantly influenced by trophic pituitary hormones

Chronic RENAL DISEASE in man and, especially, complete NEPHRECTOMY in animals, result in an increased production of parathyroid hormone. This is indicated by the development, in nephrectomized rats, of osteitis fibrosa, a lesion which is manifestly dependent upon increased parathyroid hormone formation, since *simultaneous removal* of the parathyroids with the kidneys prevents its occurrence. (See p. 546)

Shortly after the INJECTION OF PARATHYROID HORMONE, significant amounts of the principle are not demonstrable either in the blood or urine or body tissues of experimental animals, even if large doses have been given. From this it may be concluded that the substance is rapidly destroyed in the organism.

STIMULI INFLUENCING PARATHYROID STRUCTURE

Extirpation of Endocrine Glands. — As with other endocrine glands, PARTIAL REMOVAL OF THE PARATHYROIDS causes a compensatory hypertrophy of the remnant. This is of some clinical importance because it explains why the tetany after goiter operations, with accidental or voluntary removal of parathyroid tissue, so often tends to disappear within a short time.

HYPOPHYSECTOMY causes no pronounced atrophy of the parathyroids and correspondingly no signs of parathyroid insufficiency This indicates that unlike the thyroid and many other endocrine glands, *the parathyroids are* not significantly influenced by "trophic" hormones of *the pituitary.*

PANCREATECTOMY, especially if combined with hypophysectomy (as in the "Houssay dog"), may cause sclerosis and even necrosis in the parathyroids, the pathogenesis of this, rather inconstant, change has not been clarified as yet.

THYROIDECTOMY is difficult to perform without some damage to the internal parathyroids, but the external parathyroids, especially in species in which they are located at some distance from the thyroid, are not necessarily influenced by the direct effect of the trauma. Yet, in such instances, histologic changes in the parathyroids have often been noted. Special importance has been ascribed to the occasional occurrence of follicle formation in the parathyroids of thyroidectomized animals and man Exceptionally, such follicles are also seen in normal parathyroids Their appearance after thyroidectomy has given rise to the erroneous theory that there are such close similarities between the parathyroids and the thyroid that the former may substitute for the latter, if necessary. There is no reason to believe, however, that the parathyroids can ever produce thyroid hormone-like principles and the

duced by high phosphorus diets or lack of ultraviolet light.

Rays. — Using different types of filters, it was possible to demonstrate that ultraviolet light alone, does not prevent parathyroid enlargement in vitamin D deficient chicks, but daily irradiation with an air-cooled mercury arc is effective in this respect. Further work is required to elucidate the exact mechanism through which rays influence the parathyroid cells.

In mammals, radiation causes less constant changes in the parathyroids unless lack of ultraviolet light results in rickets.

DISEASES OF THE PARATHYROIDS

MALFORMATIONS

Complete APLASIA of the parathyroids is extremely rare and usually accompanied by multiple and severe malformations in other organs. It is incompatible with postnatal life.

The size of the parathyroids is so variable that true HYPOPLASIA cannot be recognized readily unless it is extremely severe. In patients suffering from so-called "pluriglandular insufficiency" or "multiple endocrine sclerosis", the parathyroids are commonly affected. With any type of parathyroid sclerosis, the possibility must be kept in mind that the connective tissue proliferation may be merely the end result of a chronic inflammatory lesion, such as tuberculosis or syphilis In most instances, differentiation between a hypoplasia, a true malformation, and secondary atrophy is impossible on morphologic grounds.

HYPERPLASIA of the parathyroids is discussed in the chapter on Clinical Hyperparathyroidism (p 577) and in connection with the various agents which stimulate the proliferation of these glands. "Nodular hyperplasia" of the parathyroids represents a transition between true hyperplasia and adenoma formation The mechanism through which hyperplasia of parathyroid tissue develops is not as yet elucidated but it is doubtful whether it ever occurs as a true congenital malformation.

ACCESSORY ECTOPIC PARATHYROIDS are very common in most animal species, except in the cat and dog, in which their incidence is only about 2-3%. In man, they are probably more common than accessory accumulations of any other glandular tissue. An exact knowledge of their usual location is of great practical importance since they are often the site of tumor formation and then must be removed in order to cure the resulting hyperparathyroidism. In addition to the occasional occurrence of accessory parathyroids in the thyroid itself, parathyroid nodules are frequently found in man between the thyroid and the thymus or in the thymus itself. This tendency to migrate caudad with the thymus is due to the close embryologic relations between the latter and parathyroid III (See p 695.)

The malformations of the parathyroids do not necessitate any therapy unless they give rise to hypo- or hyperparathyroidism (see pp 562-592).

VASCULAR LESIONS

HEMORRHAGES into the parathyroids are frequent in newborn infants and have been attributed to the trauma of birth.

ATHEROSCLEROTIC changes are not unusual in the parathyroids of aged individuals but do not noticeably impair the function of the glands

DEGENERATIONS

Whether the intracellular fat accumulations, frequently seen in the parathyroids, can be interpreted as true FATTY DEGENERATION, remains undecided. Outside of the earliest in-

In SCLERODERMA, parathyroid enlargement, sometimes with the formation of actual adenomas, has occasionally been reported. Although such changes are by no means a constant accompaniment of the disease, they deserve attention in view of the experimental production of a scleroderma-like disease by parathyroid hormone overdosage in the rat and in view of the frequent association of scleroderma and metastatic calcification in man.

In a variety of KIDNEY DISEASES, especially in chronic nephritis accompanied by "renal rickets," the parathyroids are enlarged and the accompanying bone changes are most probably due to this hypertrophy with the resultant hyperparathyroidism.

Diet. — High phosphorus, low calcium diets, especially if they are also poor in vitamin D, cause marked enlargement of the parathyroids in the fowl. Lack of ultraviolet rays sensitizes the birds to this effect of such diets.

In mammals these changes are less constant but, in general, rachitogenic diets are conducive to some parathyroid enlargement, similar to that seen in the spontaneous rickets of man.

Nervous Stimuli. — Denervation of the parathyroids (periarterial sympathectomy) has been practised for therapeutic reasons to decrease their hormone production. There is however, no definite experimental evidence to show that the innervation of the glands has any pronounced influence upon their function. Transplanted parathyroids (whose nerves have been completely severed, of course) appear to function normally.

Age. — The size of the human parathyroids increases approximately in proportion with the body weight up to about the 20th year of age; after this they remain fairly stationary. In senile individuals, there is a slight decrease in the size of the parathyroids; this is accompanied by fatty infiltration of the stroma and the occasional development of colloid cysts in the parenchyme.

Sex. — There is no pronounced sex difference in the structural appearance of the parathyroids although, both in animals and in man, the parathyroids of females tend to be somewhat larger than those of males.

Sexual Cycle. — No definite parathyroid changes are observed during estrus and menstruation in mammals but in the fowl there is a definite enlargement of these glands during the egg-laying season. This is accompanied by hypercalcemia and probably related to the formation of calcified egg shells.

Pregnancy and Lactation. — During pregnancy and lactation the parathyroids of most species, including man, show histologic signs of hyperactivity. This is in agreement with the previously mentioned fact that during pregnancy and lactation, parathyroidectomy is especially conducive to acute tetany because of an increased calcium requirement for the fetus or the nursing offspring.

Seasons. — In amphibia, the parathyroids are more compact and smaller *during the winter than during the summer season* In mammals, seasonal variations in parathyroid structure are less obvious, in birds they are striking

Drugs. — FLUORINE, which causes pronounced bone lesions, tends to produce fatty degeneration and hemorrhages in the rabbit's parathyroids

IODINE has no characteristic effect upon the parathyroids, comparable to that which it exerts upon the thyroid

STRONTIUM intoxication, which induces a type of rickets in animals, is often accompanied by parathyroid hyperplasia.

VITAMIN D OR TACHYSTEROL, given in toxic doses, depress mitotic proliferation in the parathyroids and prevent the parathyroid hypertrophy normally in-

denced only by special function tests or at times of severe strain upon calcium metabolism (e g., pregnancy, lactation, low calcium intake).

The differentiation between these two types is not always clear-cut and even in latent tetany, minor manifestations must be evident before the patient consults a physician.

According to ETIOLOGY, we distinguish between:

(1) Hypoparathyroidism due to spontaneous, primary diseases of the parathyroids (e.g., hemorrhages).

(2) Hypoparathyroidism due to operative damage to the parathyroids (e.g., postoperative tetany).

(3) Relative hypoparathyroidism, due to excessive strain upon calcium metabolism in the presence of normal parathyroids (e.g., tetany caused by low calcium intake, rickets, acidosis).

(4) "Idiopathic tetany," due to hypoparathyroidism of unknown etiology.

Obviously, all these systems of classification overlap inasmuch as any one case may be manifest or latent, irrespective of its etiology, it may occur in various age groups, etc.

PATHOLOGIC ANATOMY

The tetany of newborn infants is frequently associated with hemorrhages into the parathyroid tissue. Such hemorrhages are also quite common in normal newborn infants; yet it must be admitted that severe intraglandular bleeding could interfere with the function of the parathyroids and thus induce a predisposition for tetany These hemorrhages —which are usually ascribed to trauma incurred during the process of delivery — may give rise to secondary sclerosis with pigment deposition. Such secondary changes have been held responsible for the occurrence of delayed tetany some time after birth.

In rare instances, a parathyroiditis or fatty degeneration of the parathyroids, was found in tetanic patients, but these are quite exceptional causes of the disease.

Destruction of the parathyroids by malignant tumors hardly ever affects all glands sufficiently to cause clinical signs of insufficiency.

INCIDENCE

There are no reliable statistical data concerning the GENERAL INCIDENCE of spontaneous tetany. It may be stated, however, that the frequency of the disease is inversely proportional to the AGE of the patient, being most prevalent among newborn infants and least common in adults.

It has already been mentioned that in adults parathyroid deficiency is most frequent during PREGNANCY and LACTATION because of the increased calcium requirements at these times.

The GEOGRAPHIC DISTRIBUTION of the disease is not characteristic. Yet in northern countries, where solar radiation is less intense, it appears to be somewhat more common than in the sunny, southern lands, probably because vitamin D deficiency (more prevalent where sunlight is scarce) predisposes to tetany.

The dependence of tetany upon DIETARY factors (e.g., vitamin D, calcium, phosphorus) casts some doubt upon the interpretation of familial hypoparathyroidism as a HEREDITARY disease, since members of the same family usually eat the same diet

The incidence of POSTOPERATIVE tetany has considerably decreased with the introduction of modern thyroidectomy technics in which great care is taken to preserve the parathyroids.

PATHOGENESIS

By definition, hypoparathyroidism is due to an insufficient supply of parathy-

fancy, the human parathyroid cells are always fairly rich in lipid granules.

It has been mentioned already that as age progresses the stroma of the glands becomes increasingly more infiltrated with common fat tissue. In rare instances, a "pseudohypertrophy" of the parathyroids has been found to result from excessive lipomatosis.

AMYLOIDOSIS of the parathyroids occurs usually as part of generalized amyloidosis. It rarely causes any deficiency symptoms although it may produce some pressure atrophy of the epithelial cells.

Excessive GLYCOGEN storage is frequently noted in the parathyroids of patients suffering from tetany, but it also occurs in a number of other diseases (pernicious anemia, diabetes, septicemia, nephritis, pneumonia, amyloidosis, liver cirrhosis, etc.) and hence, must be regarded as a rather non-specific change. It is doubtful whether excessive glycogen storage should be classed as a degenerative lesion.

COLLOIDAL DEGENERATION is a condition in which the granules of the oxyphil cells seem to fuse, forming an eosinophilic homogenous cytoplasm which envelops a pyknotic nucleus. This, as well as the so-called HYDROPIC DEGENERATION and the PIGMENT ATROPHY of the parathyroids are rare degenerative lesions due to unknown causes and of doubtful functional significance.

INFLAMMATIONS

NON-SPECIFIC INFLAMMATORY LESIONS, in the sense of a "parathyroiditis" are rather common, but it is difficult to distinguish true chronic inflammations from simple sclerosis in the parathyroids.

Occasionally, SYPHILITIC GRANULOMAS or isolated TUBERCLES (as part of miliary tuberculosis) are found in the parathyroids but signs of parathyroid insufficiency do not usually result from any type of inflammatory lesion in the glands.

HYPOPARATHYROIDISM

DEFINITION

Hypoparathyroidism is a condition in which the hormone production of the parathyroids is sufficiently diminished to cause detectable deficiency manifestations, at least (as in latent tetany) at times when the requirement for parathyroid hormone is high. — Parathyroid tetany is the condition of spasmophilia which usually accompanies Hypoparathyroidism.

CLASSIFICATION

The clinical types of hypoparathyroidism may be classified according to various points of view. According to the AGE OF ONSET, we may distinguish between :

(1) Tetania neonatorum (in which hypoparathyroidism is manifest soon after birth).

(2) Childhood tetany.

(3) Adult tetany (usually postoperative).

This classification is justified because the etiology of the condition is usually different in the three age groups. Tetania neonatorum is usually associated with hemorrhages into the parathyroids, childhood tetany is mainly conditioned by the great calcium avidity of the growing skeleton, which requires a particularly high level of parathyroid function, while the tetany of adults is almost invariably due to surgical removal of the parathyroids during operations for goiter.

According to the INTENSITY OF THE INSUFFICIENCY, we may distinguish :

(1) Manifest tetany in which the signs of hypoparathyroidism are obvious without provocation.

(2) Latent tetany in which neuromuscular hyperexcitability is evi-

ing of bone fractures. The histologic appearance of the bones, however, is not very characteristically influenced although the general development of the skeleton is subnormal. Often there are coincidental rachitic lesions, merely because hypoparathyroidism tends to develop, with particular frequency on rachitogenic diets.

The TEETH of patients, who acquired *their hypoparathyroidism during adult* life, rarely show any characteristic lesions. However, if parathyroid deficiency develops at the time of teething, *rather typical, dark, transverse ridges* are formed in the enamel. The teeth which should have developed, when the hypoparathyroidism was manifest, may be *entirely absent.*

Cardiovascular System. — The electro-cardiogram (E C.G.) of tetanic patients is characterized by a lengthening *of the Q-T interval* to about 0 30-0.34 seconds (normal, 0.26-0.28 seconds) This change disappears within a few minutes after the intravenous injection *of calcium* gluconate, even in patients with very chronic tetany. Hence, the lesion is certainly not of organic nature but merely a functional disturbance due *to lack of ionized calcium.* This change in the E C.G. is not specific for hypoparathyroidism; it may also occur in certain types of hepatic coma, uremia and in *spasmophilia of extraparathyroid* origin.

Respiratory Organs. — The thoracic musculature may participate in the tetanic *contractions and thus render* breathing very difficult. Another common cause of respiratory difficulties in *tetany is* the LARYNGOSPASM, which is especially common *in children* It is due to contraction of the glottis and tends to impede particularly the inspiration of air. It may be so intense as to cause marked cyanosis and even death from asphyxia, especially if it is accompanied by a spastic contraction of the diaphragm. Usually, *however, just when* cyanosis becomes *threatening*, a forced *inspiration occurs which is accompanied* by a high pitched "crowing" sound (inspiratory stridor or laryngismus stridulus). The laryngospasm is often *elicited by* emotional *stimuli, the* ingestion of cold water or other comparatively slight irritants.

Muscles and Nervous System. — The relative rôle played by the muscular and nervous system, in the causation of the tetanic convulsions, is not definitely known, hence the motor disturbances will be discussed conjointly, irrespective of their origin In the event *of manifest tetany, spasms usually* begin with fibrillary contractions in single muscles or muscle groups and eventually develop into generalized intense spastic contractions, sometimes *involving the entire muscular system.* Almost any muscle group may be affected but most commonly, the painful tonic spasms show a definite predilection for the *muscles of the limos and face*, although those of the abdomen, trunk and neck may also be involved. The convulsions last a few minutes to several hours and may *eventually* cause *general* numbness and paresthesias throughout the body. They are often accompanied by the laryngospasms and contractions of the thoracic musculature, which — as stated above — cause severe respiratory difficulties.

The muscular contractions are *frequently preceded or accompanied by* PARESTHESIAS (e.g , tingling sensations in the lips or fingers), tenseness of the facial muscles and often there is intense *muscular pain.*

The posture of patients with CARPOPEDAL SPASM is very characteristic. The wrist and elbow are flexed, the thumb *is placed in the palm, the fingers being* rigidly flexed at the metacarpophalangeal but extended in the interphalangeal joints. This is designated as "obstetric position" or "main d'accou-

roid hormone; this may be absolute or relative.

ABSOLUTE PARATHYROID HORMONE DEFICIENCY may be occasioned by any of the various lesions discussed in the chapter on pathologic anatomy, or by surgical removal of parathyroid tissue. Irradiation of the neck region is an exceptional cause of hypoparathyroidism because the parathyroids are comparatively resistant to X-rays.

RELATIVE HYPOPARATHYROIDISM may result from a variety of conditions, which decrease the amount of ionized calcium in the blood. These will be discussed under Diagnosis (pp. 568-569) since, from the endocrinologist's point of view, their main significance lies in their differentiation from primary, absolute hypoparathyroidism.

The pathogenesis of the individual manifestations of hypoparathyroidism will be studied in the chapter on the Clinical Course (see below), in conjunction with the individual symptoms and signs. It may be stated here, however, that most of these manifestations have definitely been proven to be merely consequences of the characteristic disturbance in calcium and phosphate metabolism.

CLINICAL COURSE

State. — The appearance of the typical hypoparathyroid patient is characterized mainly by a greatly increased irritability of the neuromuscular system (spasmophilia), with a tendency to develop painful, tonic spasms of the musculature under the influence of comparatively slight external stimuli. The spasms and convulsions occur intermittently in the form of the so-called tetanic seizures or crises and are frequently accompanied by paresthesias.

The condition of tetanic patients is aggravated by a variety of agents which tend to decrease the ionized calcium content of the blood, for instance, calcium or vitamin D deficiency, excessive loss of calcium through the stools (as in diarrhea, non-tropical sprue, steatorrhea) pregnancy, lactation, rapid somatic growth (in children), alkalosis (due to excessive vomiting, pyloric obstruction, hyperventilation, injection of alkaline solutions) or ingestion of excessive amounts of phosphate (e.g., infants fed on cow's milk, which is rich in phosphorus). Phosphate retention, due to renal failure, rarely causes tetany even if the blood calcium falls to very low levels, partly because this hypocalcemia is due mainly to a diminution of the organic blood calcium and partly also because the accompanying acidosis exerts an anti-tetanic effect.

Metabolism. — The metabolic changes characteristic of hypoparathyroidism in man are so similar to those produced by parathyroidectomy in animals, that they do not deserve a separate detailed description. There is a pronounced decrease in the ionized CALCIUM concentration of the blood accompanied by hyperphosphatemia, but the rise in blood PHOSPHATES is much less constant and pronounced, than the fall in blood calcium. Calcium elimination through the urine is diminished, or even abolished; the urinary phosphate excretion is likewise low, except if the phosphorus intake is very high. The fecal calcium and phosphate elimination are not significantly changed. The calcium and phosphate content of the skeleton may be normal but is more commonly diminished, especially — as is frequently the case — if parathyroid insufficiency develops in rachitic children or in women during pregnancy or lactation. The blood PHOSPHATASE concentration is normal.

The ALKALI RESERVE of the blood tends to be diminished in tetany but no OTHER METABOLIC DISTURBANCES are characteristic.

Growth and Bone Structure. — Hypoparathyroidism retards skeletal growth in children and delays the heal-

contraction of the orbicular, superciliary and frontal muscles.

(7) LUST: tapping the peroneal nerve causes muscular contraction

(8) SCHLESINGER: tapping the tibia causes muscular contraction

(9) SCHULTZ: tapping the tongue causes it to be depressed, forming a concave upper surface

(10) HOFFMAN: immediate local pain elicited by mechanical irritation of the trigeminal, due to hyperexcitability of the sensory nerves.

The tendency of latent tetanic patients to exhibit the various types of muscular contractions described above is often referred to as "spasmophilia"

In CHRONIC TETANY, *paresthesias* are particularly common and may be accompanied by weakness, fatigability and general nervousness with only occasional attacks of carpopedal spasms

Roentgenologically demonstrable symmetric calcifications in the basal ganglia, adjacent to the lateral ventricles, may also occur in chronic tetany, *this sometimes causes epilepsy*

Sense Organs. — CATARACTS, similar to those seen in parathyroidectomized animals may occur even in young patients *suffering from idiopathic or* postoperative tetany. The blood calcium may remain normal, although the calcium content of the crystalline lens is considerably *increased. Both the zonular* and the central forms may occur (as shown by slit-lamp examination). The former is more commonly found among *young and the latter among* old patients, who are also subject to the, predominantly central, senile cataracts

In vitro experiments suggest that an increased calcium *affinity of the crystalline* lens is of etiologic significance. However other factors may also be involved *since*, if protected from solar radiation, parathyroidectomized animals appear to be resistant to cataract formation.

From a *differential diagnostic point* of view, it is well to bear in mind that cataract formation is not a specific result of parathyroid insufficiency. It may also occur in other diseases conducive to hypocalcemia (e.g., steatorrhea), *indeed the senile, diabetic and myotonic* cataract, as well as that sometimes associated with mongoloid idiocy, are unaccompanied by an obvious disturbance *in calcium metabolism.*

Correction of the other manifestations of parathyroid insufficiency by parathyroid hormone treatment does not cure the tetanic cataracts, once formed they are amenable only to surgical therapy, although their development can be prevented by suitable prophylactic hormone administration.

As part of the general neuromotor hyperexcitability syndrome, the CILIARY MUSCLE *of the iris is subject to spastic* contractions.

Digestive System. — The smooth musculature of the gastrointestinal *tract is also affected by the generalized* neuromuscular disturbance characteristic of tetany. There may be difficulties of deglutition, due to spastic contractions of the esophagus and abnormal peristaltic movements of the gastrointestinal tract may cause pain and *persistent vomiting.*

Skin and Appendages. — As a result of trophic disturbances, hypoparathyroid patients are especially subject to ECZEMA.

The HAIR is frequently lost but tends to grow back after parathyroid hormone *treatment*

The NAILS are striated, brittle and often there is necrosis of the nail root.

Urinary System. — Spastic contraction *of the urinary bladder sphincter* may cause anuria, while spasms of the smooth musculature in the wall of the bladder tend to produce enuresis.

Accessory Sex Organs. — Parathyroid insufficiency causes no specific changes in the accessory sex organs, *although their development is often sub*normal, owing to the poor general condition of the afflicted patients.

cheur." Simultaneously the feet may be bent down in an equino-varus position.

As we shall see later, the irritability of the SMOOTH MUSCULATURE is also augmented.

In the tetanic state, there is an increase in the CHRONAXIA and a decrease in the RHEOBASE of the nerves.

In latent tetany, muscular contractions are readily elicited by mechanical, electric and other stimuli. This increased irritability of the neuromuscular system is the basis of numerous DIAGNOSTIC SIGNS which are usually designated by eponyms. These are the signs of ·

(1) TROUSSEAU : when the arm is circularly compressed (manually or with a tourniquet) above the elbow, the fingers and hands assume the typical "obstetric position" (see above).



Carpopedal spasm in tetany. Typical appearance of accoucheur's hands" during a spasm (Courtesy of Dr E.-J Kepler.)

(2) KAHN AND FALTA · vasoconstriction, which results in anemia of the fingers, while Trousseau's sign is elicited

(3) ERB . production of neuromuscular responses, with galvanic currents of lesser intensity than are necessary to elicit them in normal individuals. Usually this test is performed by stimulating the median nerve (in adults) or the peroneal nerve (in children) with a current of known intensity. Contraction of the muscles is elicited by a cathodal opening current (C.O.C.) of less than 5 milliamperes in tetany but not in the normal individual. Furthermore, in hypoparathyroidism the minimal anodal opening current (A.O.C.) necessary to elicit a response is less than the minimal effective anodal closing current (A.C.C.). The reverse is true in normals.

(4) CHVOSTEK : in latent tetany, tapping the skin at the middle of the line uniting the external meatus with the angle of the mouth, elicits a twitch of the facial muscles, due to increased irritability of the facial nerve.



Hypoparathyroid tetany. Picture taken while Chvostek sign was elicited (After W M Yater Fundamentals of Internal Medicine Appleton-Century Publ 1944.)

(5) ESCHERICH tapping of the skin at the angle of the mouth causes forward propulsion of the lips

(6) WEISS : tapping of the temporal branch of the facial nerve causes

or of alkalinizing foods. Chlorides are lost through the gastric secretion or vomitus (*gastric tetany*) and unlike in true parathyroid tetany, the blood CO_2 is greatly diminished, the blood calcium and phosphate levels are usually normal and the urine contains calcium. — In gastric tetany, the blood phosphate concentration may be raised.

(6) PHOSPHATE TETANY. As in parathyroid tetany, the blood calcium is reduced, the blood alkali reserve is normal and the blood phosphate concentration increased. However, the past history reveals an excessive intake of alkaline phosphates. The condition can be produced experimentally by intravenous administration of Na_2HPO_4 or K_2HPO_4. A neutral mixture of acid and alkaline phosphates causes *no reduction in the ionized calcium concentration* of the blood and consequently no tetany.

(7) HYSTERIC CONVULSIONS. In hysteria there may be muscular spasms which simulate parathyroid tetany but are unaccompanied by other signs of hypoparathyroidism. Usually, the motor manifestations are exclusively of psychic origin but they can be secondary to hysteric hyperpnea.

(8) EPILEPSY. The paresthesias, which often precede the convulsions in true hypoparathyroid tetany, are often mistaken for the aura of epilepsy. It must also be kept in mind that epilepsy and parathyroid tetany may develop in the same *patient*. However, the absence of any calcium and phosphate metabolism disturbance and the inefficacy of parathyroid hormone treatment in true epilepsy, facilitate the recognition of this disease.

(9) UREMIA Uremic convulsions may be confused with hypoparathyroid tetany, however, in this case, the accompanying hypocalcemia is secondary to the hyperphosphatemia caused by insufficient renal phosphate elimination The coexistence of the classic signs of nephropathy *facilitates the diagnosis.*

(10) PSEUDO-HYPOPARATHYROIDISM ("SEABRIGHT-BANTAM SYNDROME" OF ALBRIGHT ET AL.). A few patients have been described in whom the clinical and biochemical findings were similar to those seen in hypoparathyroidism, but they proved resistant to parathyroid extracts and relatively resistant to A.T.10 treatment. They usually have a peculiar appearance (round-face, rather thick set figure). (See pp. 570-572.) The term "seabright-bantam syndrome" was chosen to describe them because here, as with the plumage of the bantam fowl, the cause of the anomaly is an insensitivity of the target organ (cf p 621)

(11) INTOXICATION WITH ATROPINE, LEAD OR STRYCHNINE The past history of poisoning and the absence of any disturbance in calcium and phosphate metabolism permit differential diagnosis

(12) INFECTIONS SUCH AS MENINGITIS OR TETANUS. Calcium and phosphate metabolism remain normal and there are symptoms characteristic of these infections.

(13) HEAT CRAMPS These occur only in patients exposed, for long periods, to high temperatures They are unaccompanied by any of the typical manifestations of hypoparathyroidism

PROGNOSIS

While in newborn infants, hypoparathyroid tetany due to trauma at birth is often fatal, the tetany of older children tends to be mild or latent Even in severe childhood tetany, transitory parathyroid hormone, or vitamin D treatment with a high calcium diet is usually sufficient therapy since eventual spontaneous recovery is the rule In postoperative *tetany, temporary* treatment may also suffice if an adequate amount of parathyroid tissue is left in place to maintain an approximately normal blood calcium level, at least until after compensatory hypertrophy can occur.

Complete parathyroidectomy necessitates continuous treatment and even so, the eventual prognosis is bad.

COMPLICATIONS

The most serious complications of hypoparathyroidism occur during the tetanic crises. At this time in children a laryngospasm may be fatal and violent convulsions may cause bone fractures. Other complications are rare

DIAGNOSIS

If there is manifest tetany, the diagnosis of hypoparathyroidism is comparatively simple on the basis of the characteristic clinical manifestations described above. The fibrillar and spastic contractions, the difficulty of swallowing, the inspiratory stridor, the awkwardness of the movements when the patient is asked to perform simple manual tasks (handling of scissors, carrying a full glass of water), the *intermittent occurrence of convulsive crises*, the paresthesias and the trophic disturbances are of special diagnostic interest. — In the event of latent tetany, the neuromotor disturbances must be provoked by special function tests (see pp. 565-567).

A past history of thyroidectomy (in the adult) or a birth trauma (in the new-born infant) will call attention to a possible parathyroid lesion as the etiologic factor. The development of spastic convulsions during pregnancy (in the absence of eclampsia) or lactation should always raise the suspicion of a latent, chronic parathyroid insufficiency.

The most important biochemical change is the decrease in ionized blood calcium. All neuromotor disturbances disappear following correction of this disturbance by parathyroid hormone

Calcium is not eliminated in the urine if the blood concentration falls below the threshold level of about 6 mg.%, hence even the mere qualitative determination of urinary calcium is informative. This may readily be done with the Sulkowitch reagent (oxalic acid 2 5 gm., ammonium oxalate 2 5 gm., glacial acetic acid, 5 cc., made up with distilled water to a volume of 150 cc) this forms a milky precipitate of calcium oxalate with urine which contains calcium. The amount of the precipitate gives a visible index of the approximate quantity of calcium present. In the absence of urinary calcium elimination, a clinical syndrome of tetany is most probably due to parathyroid insufficiency.

Before assuming that a syndrome of tetany is of parathyroid origin, the following conditions must be considered for differential diagnosis:

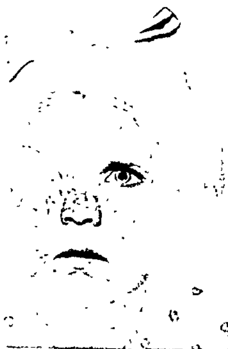
(1) Rickets and osteomalacia. There is a past history of dietary calcium or vitamin D deficiency. The calcification of the skeleton is inadequate, growth is stunted and there are bone deformities. The blood calcium is low, the blood phosphatase above normal but unlike in hypoparathyroidism, the blood phosphate level is normal or low.

(2) Sprue or celiac rickets. There is hypocalcemia, unaccompanied by hyperphosphatemia, with increased elimination of phosphorus in the urine and calcium in the feces (formation of insoluble calcium soaps of fatty acids, deficient vitamin D absorption) The stools are fatty.

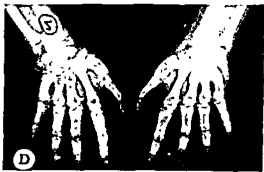
(3) "Infantile or idiopathic tetany" This syndrome may be of parathyroid origin; its symptomatology is practically identical with that of hypoparathyroidism except that the blood phosphate level is claimed to be normal or reduced.

(4) Guanidin tetany. There is a past history of guanidin intoxication. The blood calcium is normal, or slightly reduced, but the blood phosphate concentration is increased as in true parathyroid tetany.

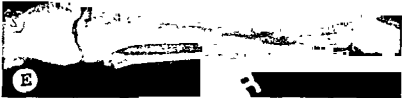
(5) The Tetany of alkalosis. *There is a history of pyloric or high* intestinal obstruction, uncontrollable vomiting, forced hyperpnea, ingestion of excessive amounts of bicarbonate.







C



Pseudo-hypoparathyroidism with epilepsy. — A. 8½-year-old girl referred for epilepsy Stocky figure, round face and peculiar hands characteristic of this syndrome. Chvostek sign markedly positive; blood calcium 4 5 mg %, phosphorus 10 22 mg %, no calcium in urine by Sulkowitch test Treatment with A T 10 raised blood calcium to 10 6 and decreased phosphorus to 6 5 mg, while Chvostek disappeared Initially abnormal electroencephalogram likewise improved under this therapy Not responsive to parathyroid hormone therapy — B. Interstitial calcification in wrist region Premature closure of the epiphyses of the elbow and bowing of the radius — C. Note short stubby hands — D. X-ray reveals shortened metacarpals in both hands — E. Spur formation on tibia (Cont'd on p 572)







Pseudo-hypoparathyroidism ("Seabright-Bantam Syndrome"). — A. *Note short stature* and round face — B. Typical appearance of stubby hands, index finger longer than other fingers. — C. X-rays of hands showing shortening of metacarpals *1, 3, 4* and *5*. *Compare* with B, and note that relatively long index finger is due to normal metacarpal 2.
(*After* F. Albright et al. Endocrinology 30: 922, 1942.)

The tetany of pregnancy and lactation usually disappears after the period of increased calcium requirement.

THERAPY

Prophylaxis. — The best therapy of hypoparathyroidism is the timely institution of prophylactic measures. Thus, in order to minimize the danger of tetany in newborn infants, it is important to insure a high calcium intake and safeguard against the ingestion of too much phosphorus (e.g., cow's milk) or of vitamin D deficiency.

The careful handling of the parathyroids and their blood vessels during operations for goiter is, of course, the *best prophylaxis against postoperative* tetany. Following slight damage to the parathyroids, in the course of such operations and *following the removal* of large parathyroid adenomas for hyperparathyroidism (compensatory atro-

caloric intake is assured by giving a diet rich in carbohydrates, fat, fruit and vegetables.

VITAMIN D_2 (CALCIFEROL) is beneficial in hypoparathyroidism because it facilitates the absorption of calcium from the intestinal tract and calcium retention by the tissues. It may be administered as such, in daily doses of 400,000 to 1,600,000 units (10 to 40 mg.) which after some time may be reduced to 120,000-200,000 units (3 to 5 mg.).

A derivative of vitamin D_2, DIHYDROTACHYSTEROL, is available in oil solution under the trade name of "AT 10" (Antitetanic Preparation No. 10). It has almost no antirachitic potency but possesses a marked and prolonged hypercalcemic effect. It is usually given in daily doses of 3 cc. (6 mg.); after some time, the dosage may gradually be reduced to 1-2 cc. per week. This preparation has the advantage over parathyroid hormone that: (1) there is no spontaneous or acquired resistance to it, (2) it can be administered orally; (3) it has a more prolonged action and (4) it is less expensive than the hormone. On the other hand, dihydrotachysterol acts more slowly than parathyroid hormone and hence, preference should be given to the use of the latter, in combination with intravenous calcium administration, if the patient is actually in a tetanic crisis.

In view of the possibility of vitamin D and dihydrotachysterol intoxication with calcification of soft tissues, it is essential to control the blood calcium continuously. Fairly accurate supervision of the dosage can be achieved by the patient himself with the aid of the Sulkowitch reagent, as outlined above (see: p. 568).

The commercial preparations of PARATHYROID HORMONE are available in sterile ampules of the aqueous extract, suitable for subcutaneous or intramuscular injection. They are usually standardized to contain 80 to 120 U.S.P. units, per cc. In severe cases, especially if the patient is in a tetanic crisis, 100 units may be administered in a single dose, or in divided doses, over 24 hours. In mild cases, 10 to 50 units, per day, will suffice. The hormone is not yet available in chemically pure form and cannot be given orally as it is destroyed by the intestinal enzymes.

In order to avoid hyperparathyroidism, the blood calcium level must be constantly checked.

Parathyroid Transplantation. — In tetany due to complete destruction or surgical removal of the parathyroids, transplantation of parathyroid tissue would appear to be the most logical therapeutic procedure, since it alone could effect a permanent cure. Unfortunately, in many instances, the transplanted parathyroids are gradually absorbed and tissue for transplantation is not readily available. However, this method deserves further trial since long term cures have been reported by transplanting the parathyroids of babies who were stillborn or died soon after birth.

HYPOPARATHYROIDISM IN ANIMALS

In lactating cows ("milk fever") and SHEEP ("lambing sickness" or "ewe distemper"), the blood calcium may fall to tetanic levels, due to excessive loss of calcium through the milk. In such instances, inflation of the udder with air, suppresses milk secretion and thus restores the serum calcium to normal and cures the accompanying tetany.

Calves reared on whole milk may develop MAGNESIUM DEFICIENCY TETANY because of the low (0.01%) magnesium content of the milk. This condition may be mistaken for parathyroid or calcium deficiency tetany. In contrast with these latter conditions, however, the blood calcium and phosphorus remain normal, furthermore magnesium administration is of curative value. Magnesium deficiency tetany does not appear to occur in man.



Mother of Patient with Pseudo-hypoparathyroidism (shown on p 571) — F. The child's mother had a mild form of the same disease Note that shortening of hands is limited to ring and small finger. There was also bowing of the radius. blood phosphorus 6.2 mg %. blood calcium normal (10.8 mg %), no epilepsy or tetany



— G. X-rays clearly show that shortening of metacarpals is limited to two fingers Note also soft-tissue calcification in the wrist region

(Courtesy of Dr J S L Browne and Department of Radiology Royal Victoria Hospital)

phy of the remaining parathyroids), it is well to prescribe routinely a high calcium, low phosphate diet and perhaps even some parathyroid hormone during the first days after the operation.

Internal Therapy. — The dietary treatment of hypoparathyroidism is based on the administration of adequate amounts of CALCIUM in a readily absorbable form, preferably as calcium chloride (4-5 gm. per day, in a 45% aqueous solution). The chloride has the added advantage of causing slight acidosis which counteracts tetany For oral use, organic salts, such as the lactate, gluconate, or carbonate, should be prescribed only if the patient tolerates them better than the chloride. Their main advantage is that, being more suitable for parenteral administration (e.g., calcium gluconate 10-20 cc. of a 10% solution intramuscularly or intravenously), they may be used for immediate relief during a crisis. However, since the effect of parenterally administered calcium lasts only about 4 to 7 hours, two to three injections per day are necessary.

The PHOSPHATE intake must be kept low by eliminating from the diet all foods which contain much phosphorus, (meat, egg yolk, cheese). An adequate

(6) Marble bone disease. The new bone formation occurs almost without any osteitis fibrosa.
(7) Scleroderma. Here fibrosis and calcification occur in the derma.

It is still highly problematic whether marble bone disease and scleroderma should be regarded as primarily of parathyroid origin. As stated elsewhere, however, there is good evidence to indicate that parathyroid hormone overdosage can produce manifestations similar to those seen in the majority of the cases of marble bone disease and scleroderma, respectively.

The so-called "osteitis fibrosa circumscripta" or localized fibrous osteitis and "Albright's syndrome" (see: p. 583-586) are not likely to be of parathyroid origin.

PATHOLOGIC ANATOMY

The most common causative lesion in hyperparathyroidism is ADENOMA formation in one or several parathyroids. These adenomas may arise from a limited region of the gland or may involve the entire parathyroid Histologically, they consist either of oxyphil or chief cells or even of intermediate types between the two. This further supports the view that the two main types of parathyroid cells are essentially equivalent Multinuclear cells and mitotic figures are often numerous in these adenomas, while lipid granules are scarce. Sometimes, one finds cystic cavities filled with colloid or blood It is especially important to remember that parathyroid adenomas tend to develop in ectopic glands and hence, the entire region between the neck and thymus must be carefully examined before assuming that a case of "functional hyperparathyroidism" is unaccompanied by morphologic changes in the parathyroids.

In most cases, parathyroid adenomas measure only about 2 to 3 cm in diameter, but sometimes — especially if they become the site of cyst formation — they reach a diameter of 10 to 15 cm. or more. A microcystic thyroid-like variety of the parathyroid adenoma has been described under the name of "PARATHYROID STRUMA"

In DIFFUSE HYPERPLASIA of the parathyroids, the cell number is greatly increased in all four glands, but otherwise there are no conspicuous structural abnormalities Conversely, HYPERTROPHY of the parathyroid cells is often accompanied by a conspicuous increase in the cytoplasm, the latter becomes clear and is surrounded by a rather eosinophilic cell membrane The nucleus does not participate equally in this enlargement and the total number of the cells remains essentially normal.

There are many intermediate types between diffuse hyperplasia and adenoma formation. These are sometimes designated as "NODULAR HYPERPLASIAS"

INCIDENCE

The GENERAL INCIDENCE of hyperparathyroidism is low. Perhaps the disease is not as rare, however, as was originally assumed, especially if it is correct, as some investigators believe, that 3 to 5% of all kidney stones are of hyperparathyroid origin.

The disease occurs with approximately equal frequency in both SEXES.

Hyperparathyroidism may occur at any AGE but is most common in middle-aged persons. It has even been claimed that true primary hyperparathyroidism never occurs before puberty

The GEOGRAPHIC DISTRIBUTION of hyperparathyroidism has not been studied adequately as yet, but the disease is manifestly more frequent in northern than in southern countries, perhaps because in the north, ultraviolet rays are scarce and rickets common

PATHOGENESIS

The pathogenesis of parathyroid adenomas is not known. It is probable,

HYPERPARATHYROIDISM

SYNONYMS referring to the most common type in which the skeletal system is involved: osteitis fibrosa cystica, v Recklinghausen's disease, osteodystrophia fibrosa, parathyroid osteosis. — The resulting calcium precipitation in soft tissues is described as: calcinosis universalis, metastatic calcification or calcium gout.

DEFINITION

Hyperparathyroidism is a condition in which the hormone production of the parathyroids is sufficiently increased to cause detectable overdosage symptoms. Although bone changes are present in the great majority of the cases, hyperparathyroidism is not necessarily accompanied by osteitis fibrosa.

CLASSIFICATION

It is customary to classify the clinical types of hyperparathyroidism either according to etiology or according to the most prominent manifestations

According to ETIOLOGY, we distinguish:

(1) Primary hyperparathyroidism due to:
  (a) Parathyroid adenomas
  (b) Diffuse parathyroid hyperplasia
  (c) Overdosage with exogenous parathyroid hormone. This form is seen in patients who, for therapeutic reasons (e.g., in tetany) received an excessive amount of parathyroid hormone, because the dosage was not adequately controlled.

(2) Secondary hyperparathyroidism (resulting from an increased requirement for parathyroid hormone). This may be occasioned by:
  (a) Renal insufficiency ("renal rickets," "renal fibrocystic osteosis," "renal osteitis fibrosa"). Here chronic renal failure causes bone lesions somewhat reminiscent of those seen in rickets but actually due to osteitis fibrosa Excess parathyroid hormone is apparently secreted as a compensatory reaction to the hyperphosphatemia and acidosis occasioned by kidney deficiency.
  (b) Rickets and destructive bone diseases. These call for an increased production of parathyroid hormone, because of the bone destruction and the derangement of calcium and phosphate metabolism.

According to the PREDOMINANT CLINICAL MANIFESTATIONS we distinguish:

(1) Typical osteitis fibrosa in which the bone destruction is by far the most conspicuous derangement.

(2) Osteitis fibrosa with renal calculi.

(3) Renal calculi without osteitis fibrosa.

(4) Osteitis fibrosa with renal insufficiency. Here there is severe metastatic calcification in the kidney, not necessarily accompanied by the formation of renal calculi In some of the relevant cases, the bone lesions are not pronounced, especially if the calcium intake is ample The uremia may be accompanied by nausea, vomiting, debility, loss of weight, dizziness and anuria but the blood pressure is not increased. Autopsy reveals a parathyroid adenoma

(5) "Pagetoid" osteitis fibrosa. Here the new formation and destruction of bone are about equally prominent and lead to pronounced bone deformities.

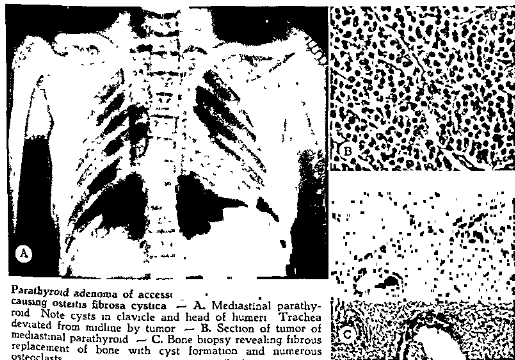
greatly diminished as a result of the osteoclastic bone destruction.

The alkaline PHOSPHATASE activity of the plasma (normally 3-4 Bodansky units) is usually increased and may rise to 20 units.

Growth and Bone Structure. – Clinically, the most conspicuous manifestations of hyperparathyroidism are the skeletal lesions. Often one of the first complaints is that the patient becomes shorter. This is due to partial collapse of vertebrae, which may also result in marked kyphosis. Spontaneous bone fractures are very common and may lead to serious deformities of the thorax, pelvis or the long bones There may also be irregular bone proliferations (usually excessive callus formation around imperceptible fractures): these lead to visible deformities, if they develop in bones situated immediately under the skin, for instance in the skull, tibia, hands or feet. The patients also complain of "rheumatic" pains in the bones and joints, especially those of the lower extremities.

X-RAYS reveal more or less diffuse or spotty decalcification of the skeleton. The calvarium is mottled, the alveoli of the teeth are distended and the layer of compact bone which lines them is irregular. The vertebrae are transparent to X-rays and often the intervertebral discs herniate into the partially collapsed bodies of the vertebrae. The marrow cavity of the long bones is enlarged and the compact shaft becomes extremely thin. The cancellous bone in the metaphyses, loses its normal structure because of the thinness and irregularity of the trabeculæ. Sometimes cystic cavities develop within the long bones.

The pelvis is frequently involved in the process of decalcification and its mottled appearance and deformed outlines are quite characteristic. Spontaneous fractures and infractions of bones are also conspicuous in the typical X-ray picture



Parathyroid adenoma of access[illegible] causing osteitis fibrosa cystica — A. Mediastinal parathyroid Note cysts in clavicle and head of humeri Trachea deviated from midline by tumor — B. Section of tumor of mediastinal parathyroid — C. Bone biopsy revealing fibrous replacement of bone with cyst formation and numerous osteoclasts

(Courtesy of Dr R.-C. Grauer.)

however, that metabolic disturbances — capable of causing parathyroid hypertrophy and hyperplasia — *may predispose* to the formation of true tumors.

Secondary hyperparathyroidism is due to a compensatory parathyroid hyperplasia and hypertrophy. This usually develops as a result of some bone lesion or metabolic disturbance which deranges calcium and phosphorus metabolism. These conditions have been studied in connection with the "Stimuli Influencing the Parathyroids."

The pathogenesis of the organ changes and metabolic disturbances, resulting from increased parathyroid hormone formation, are discussed in the sections . "Experimental Physiology of the Parathyroids" and "Clinical Course of Hyperparathyroidism."

CLINICAL COURSE

State. — The general condition of patients suffering from hyperparathyroidism is usually poor. The fragility of their bones and the weakness of their muscles tends to immobilize them, while the gastrointestinal complications interfere with their nutrition. The resulting general debility decreases resistance to various infections and intoxications so that these patients frequently succumb to comparatively mild, intercurrent diseases.

Metabolism in General.—The B.M.R. is not influenced by hyperparathyroidism, nor is there any other characteristic biochemical change except in compounds which participate in bone metabolism (calcium, phosphorus and phosphatase).

Metabolism of Calcium, Phosphorus and Phosphatase. — The BLOOD CALCIUM is characteristically increased, due to a rise in the ultrafilterable fraction. Since the protein-bound calcium is roughly proportional to the blood protein concentration, the total plasma calcium is not necessarily augmented if there is hypoproteinemia. In doubtful cases, it is important, therefore, to determine not only the total plasma calcium *but also the* plasma protein concentration, in order to estimate the level of the ultrafilterable plasma calcium. In most cases, the total plasma calcium rises to about 14-16 mg.% but sometimes, it may be as high as 20-25 mg %.

The calcium content of the cerebrospinal fluid, which is almost exclusively ultrafilterable, is increased even in those cases in which hypoproteinemia (accompanied by a decrease in protein-bound calcium) prevents an increase in total plasma calcium.

In mild, chronic cases, even the ultrafilterable calcium content of the blood may occasionally remain normal, perhaps because of such compensatory reactions as are known to occur under the influence of prolonged exogenous parathyroid hormone administration.

The inorganic BLOOD PHOSPHATE is usually low, sometimes amounting to only 2.0 mg.%. However, in the final stages of severe hyperparathyroidism, if urinary excretion of phosphates is severely impeded by renal insufficiency, there may be no drop in blood phosphates.

The *URINARY CALCIUM AND PHOS*PHORUS EXCRETION is usually augmented. It is characteristic of hyperparathyroidism that patients kept on a low calcium diet (0.1-0 2 gm. of calcium per day) excrete much more than the normal quantity, in fact about twice the amount ingested. Consequently, the calcium balance is markedly negative in hyperparathyroidism *although there is* a definite tendency for metastatic calcification of soft tissues.

This increased urinary calcium and phosphate elimination is largely responsible for the formation of the renal calculi, so frequently seen in this disease

Of course, the CALCIUM AND PHOSPHATE CONTENT OF THE SKELETON IS

time is often decreased in osteitis fibrosa and there is a great tendency towards the formation of thrombi.

The invasion of the myeloid bone marrow by fibrous tissue may so interfere with blood formation that an aplastic ANEMIA develops. This is more com*mon in marble bone disease than in* osteitis fibrosa.

Cardiovascular System. — Hyperparathyroidism is frequently accompanied by bradycardia and irregularities of the cardiac rhythm. The electrocardiogram reveals a shortening of the Q-T interval *from the normal of 0.26 to 0.28 seconds*, to as little as 0 22 seconds. All these changes are generally attributed to the hypercalcemia; they usually disappear after removal of the hyperactive para*thyroid* tissue. — *Occasionally* the arrhythmias may be the consequence of metastatic calcification in the cardiac muscle.

X-rays frequently reveal calcifications in the blood vessels. In rare instances, an ectopic parathyroid adenoma *is discovered (by radiologic examina*tion) along the arc of the aorta or in the thymus.

Lymphatic Organs. — Hyperparathyroidism causes no noteworthy changes in the lymphatic organs Calcium deposits in them are quite exceptional

Respiratory Organs. — *The only* noteworthy changes are calcification of the bronchi, and occasionally a severe thoracic deformation, due to osteitis fibrosa of the ribs and vertebræ

Muscles. — General weakness and marked atony of the musculature are rather *characteristic and early manifes*tations of hyperparathyroidism They are accompanied by diminished neuromuscular excitability and deficient coordination of the movements

Nervous *System. — The* hypercalcemia often diminishes the chronaxia, this may account at least in part for the lack of co-ordination in the patient's movements. There are also, more or less *diffuse, vague pains in the bones, joints* and abdomen. The bone pains may become so severe as to immobilize the patient.

Sense Organs. — In typical cases of hyperparathyroidism the sense organs are not involved.

Digestive System. — Constipation is a frequent manifestation of hyperparathyroidism; it may be accompanied by nausea, vomiting and anorexia. The common occurrence of gastritis is reminiscent of the gastrointestinal lesions observed in experimental hyperpara*thyroidism*

Skin. — Metastatic calcification in the skin is comparatively common and is a manifestation of the generalized tendency to calcium deposition in soft tissue. This pure metastatic calcification is sometimes difficult to differenti*ate from true scleroderma. As stated in* a previous chapter (p 557) massive doses of parathyroid hormone may cause scleroderma-like lesions in animals and it has been suggested that the spontaneous scleroderma of man may be of parathyroid origin. Para*thyroidectomy frequently produces* at least a temporary improvement in the condition of the sclerodermatous skin (Leriche) but the disease is rarely associated with an increase in blood cal*cium or a parathyroid adenoma. Prob*ably the parathyroids are not solely responsible for the cutaneous lesions

Urinary System. — The most important urologic complication of hyperparathyroidism is the development of urinary calculi, this is due, at least in part, *to increased calcium and phosphorus* elimination through the urine These calculi are so common that they possess a definite diagnostic value, especially since they are readily detectable by X-rays

Metastatic calcification is particularly frequent and intense in the kidneys. Here the calcium deposits are often so heavy that they can be detected by



Bones in osteitis fibrosa. Subcortical bone resorption in the tibia of a patient with parathyroid adenoma
(Courtesy of Dr E.-J. Kepler.)

The HISTOLOGIC APPEARANCE of the bones is particularly characteristic and hence, a biopsy specimen is of great value in diagnosing otherwise obscure cases. There is much *fibrous tissue* which so pervades the bones that the latter become pliable and can readily be cut with the knife. At the junction between the fibrous tissue and the bony trabeculæ, numerous osteoclasts are found which are manifestly absorbing bone. In addition to these destructive processes, some new bone formation is almost invariably detectable, though it is usually slight. Occasionally, however, proliferative changes may be so intense as to form hypertrophic callus tissue around small fractures.

As stated in the chapter on Experimental Physiology, chronic overdosage with small doses of parathyroid hormone causes marked *bone deposition* in experimental animals; this condition resembles marble bone disease. Perhaps the proliferative lesions in otherwise typical osteitis fibrosa, represent a transition between the latter and marble bone disease.

Especially in the metaphysis, *"giant cell tumors"* are frequently found. These consist of a fibrous stroma with many osteoclastic giant cells. In the cytoplasm of the latter hemosiderin or debris of red corpuscles tends to accumulate as a result of phagocytosis. It is because of the engulfed red cell material that these "tumors" are brownish upon naked eye inspection. *The size of the tumors varies, but they* may become so large as to deform the bone.

The bone *cysts* are essentially similar to the above-mentioned tumors, but they possess a central cavity filled with some *albuminous, coagulated fluid, hemorrhages* or — more rarely — cholesterol.

The cysts may result from the central degeneration of giant cell tumors, from lymph accumulation and edema within the fibrous tissue, or from hemorrhages with subsequent absorption of the blood. — Neither the brown, "giant cell tumors" nor the cysts are true blastomas.

The *bone marrow* may be fatty or myeloid. Sometimes, the proliferation of the fibrous tissue is so intense that blood formation is seriously impeded because of bone marrow destruction.

Joints. — Vague, rheumatoid joint pains are quite characteristic of hypoparathyroidism but it is doubtful whether one should speak — as some authors do — of a "hyperparathyroid rheumatism." Anatomic joint lesions are uncommon in this disease, although osteitis fibrosa underneath the joint surface may secondarily affect the articulations. The purported beneficial effect of parathyroidectomy in certain types of arthritis, requires confirmation.

Blood. — Perhaps as a result of the hypercalcemia, the BLOOD COAGULATION

weakness of the musculature and a marked polyuria with polydipsia are often also very disturbing.

X-rays reveal a partly generalized, *partly spotty decalcification* of the bones, sometimes with multiple bone cysts.

The blood calcium and plasma phosphatase are increased, while the blood phosphates are diminished.

A palpable parathyroid tumor in the thyroid region is rarely distinguishable.

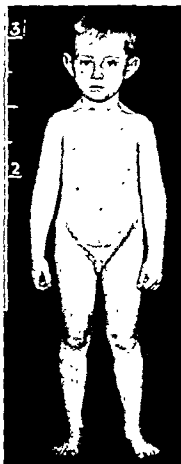
In doubtful cases, a biopsy specimen of bone or an exploratory operation may *ascertain the diagnosis.*

The following conditions must be considered for differential diagnosis:

(1) PAGET'S DISEASE. Unlike in hyperparathyroidism, the affliction of the skeleton is limited so that X-rays reveal perfectly normal areas, alternating with regions in which there is decalcification or excessive new bone formation. The blood calcium and phosphate levels remain normal but the blood phosphatase is very much augmented resemblance of Paget's disease to hyperparathyroidism may be so striking that, especially in the "pagetoid form" of the latter, a differential diagnosis may not be possible without biopsy.

(2) OSTEOMALACIA. There is pronounced and rather diffuse demineralization of the skeleton. This is due to inadequate formation and deficient calcification of new bone while the rate of bone destruction remains essentially normal. The blood calcium is unchanged or slightly below normal and the blood phosphate level, subnormal The plasma phosphatase is increased and there is a history of absolute or relative vitamin D deficiency.

(3) RENAL RICKETS. Only the past history of the patient permits differentiation between the secondary hyperparathyroidism, due to renal lesions, and the primary, accompanied by resultant kidney damage In the former condition, evidence of renal disease precedes the skeletal manifestations.



Renal dwarfism. Age 6½ years, skeletal age 4 years Height 38" (normal approximately 44"), urea clearance 19 and 20%, blood urea 60 mg %, serum calcium 9 2, phosphorus 3 9, cholesterol 200 mg., sella turcica and chest X-rays are normal

(Courtesy of Dr E P McCullagh)

there is no decrease in blood phosphates because the urinary phosphorus elimination is impeded. In the presence of severe chronic renal lesions, acidosis and an increase in blood chlorides tend to occur It will be remembered, however, that primary hyperparathyroidism may secondarily cause renal insufficiency, accompanied by the same manifestations

(4) MULTIPLE METASTATIC BONE TUMORS. These may cause hypercalcemia, increased calcium elimination through the urine and renal stones. The

X-rays and may eventually lead to dysuria, albuminuria, hematuria or even fatal uremia.

Hyperparathyroidism also causes polyuria and consequently polydipsia. The polyuria can be so severe that, in the absence of hyperglycemia and glycosuria, the condition may be confused with a true diabetes insipidus. It often leads to enuresis

The renal calculi of hyperparathyroid patients are phosphate-oxalate-calcium stones. They are probably occasioned both by the increased urinary elimination of calcium and phosphates and by the often alkaline reaction of the urine (inappropriate diet), which enhance calcium precipitation. The presence of cellular débris, protein clots or inflammatory exudate in the urinary passages is important since it helps the precipitation of the calcium salts in cohesive masses; otherwise the precipitate would be eliminated in the form of sand. The urinary calculi are sometimes responsible for terminal anuria in hyperparathyroidism; however, this may also be due to intense and diffuse metastatic calcification, within the renal parenchyme.



Renal calculi in hyperparathyroidism. Note shadows of two large bladder-stones in a patient with parathyroid adenoma In this case there was no manifest bone disease

(Courtesy of Dr E -J Kepler)

Accessory Sex Organs. — Changes in the sex organs rarely accompany hyperparathyroidism. Testicular atrophy, or menstrual disturbances, which are occasionally seen in patients whose general condition is severely affected by advanced hyperparathyroidism, are probably of non-specific nature.

COMPLICATIONS

The most important complications of hyperparathyroidism are the multiple bone fractures and intercurrent diseases due to the bed-ridden condition of patients whose skeletal system is severely affected.

PROGNOSIS

Spontaneous cures do not occur but *there may be prolonged remissions* in the course of clinical hyperparathyroidism.

The postoperative prognosis is excellent if the hyperparathyroidism is due to circumscribed parathyroid tumors which can be completely removed. On the other hand, the ablation of one to three normal parathyroids hardly ever produces a noteworthy improvement. If the orthotopic parathyroids appear to be normal, the cause of hyperparathyroidism is almost invariably an ectopic parathyroid tumor, for which a careful search must be made

DIAGNOSIS

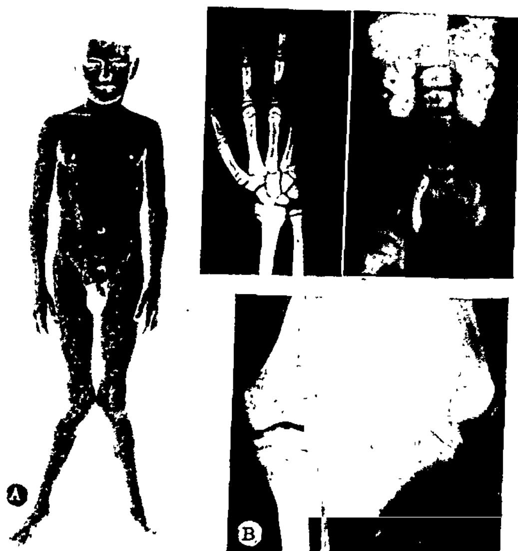
In typical cases, the diagnosis is readily made on the basis of the most characteristic manifestations

The typical hyperparathyroid *patient* is middle-aged, complains of diffuse bone and joint pains and spontaneous fractures precipitated by extremely mild traumas; he often states that he is "growing shorter" There are gastrointestinal disturbances, especially constipation, anorexia, abdominal pain, nausea and vomiting The generalized

(6) ALBRIGHT'S DISEASE. (Localized osteitis fibrosa, polyostotic fibrous dysplasia). This is a syndrome of disseminated, fibrous dysplasia of the bones, with irregular areas of skin pigmentation and, in females, with precocious puberty. It is often accompanied by hyperthyroidism. The blood calcium, phosphate and phosphatase levels are usually normal but there may be a rise in blood calcium and phosphatase. This is apparently a congenital disease, and is not of parathyroid origin. Localized osteitis fibrosa alone is not designated as Albright's disease.



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(Courtesy of Dr R C Grauer)



Renal Rickets with dwarfism. — A. 15-year-old boy, height 56" (normal 59 6"). Extreme genu valgum There was severe anemia and albuminuria, blood urea · up to 219 mg %, calcium 9 5 mg %, phosphatase 6 8 Bodansky units, acidosis with greatly reduced CO_2-combining power Autopsy revealed striking hyperplasia of 5 parathyroid glands — B. X-rays show irregular, furry appearance about the epiphyseal lines in lower radius, lower femur and upper tibia Extreme hydronephrosis due to urethral constriction near the bladder orifice.

(Courtesy of Dr E.-P McCullagh)

blood phosphate level, however, is usually normal and there is rarely any pronounced increase in blood phosphatase Characteristically, only focal lesions are seen in the skeleton; outside of these, the osseous system remains normal A search for the primary neoplasm may reveal the presence of one of the cancers which have a particular tendency to metastasize in bone (e.g., mammary, prostate, bronchial, thyroid or renal cancers).

(5) MULTIPLE MYELOMAS. These usually lead to very sharply circumscribed bone defects, which upon X-ray examination, resemble air bubbles within the bone. They tend to occur especially in the ribs, sternum or vertebræ and frequently cause urinary elimination of Bence-Jones's protein, rise in plasma globulin, anemia and renal insufficiency. A biopsy of the sternal bone marrow may help to ascertain the diagnosis.

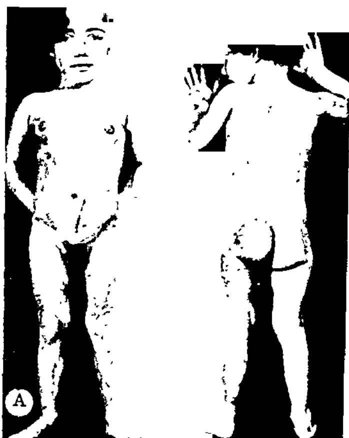








Polyostotic fibrous dysplasia (Albright's Syndrome) — A Rare occurrence in a boy (4 years of age) Note unilateral congenital melanin pigmentation of skin Atrophy of right leg due to disuse from disabling cystic bone disease — B X-ray of pelvis shows cystic bone disease Note softening causing change in neck of right femur (Courtesy of Dr R -C Grauer)



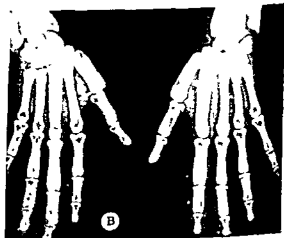






Polyostotic fibrous dysplasia (Albright's syndrome). (After F Albright et al New England J Med *216* 727 1937.) — A Photograph of patient at the age of 3 years 9 months Note marked precocity and areas of pigmentation — B X-ray of hand Note involvement of all metacarpals and phalanges with normal carpal bones and normal epiphyses — C X-ray of skull Note characteristic marked density in base of skull — D Hyperparathyroidism X-ray of skull Compare with Fig C Note generalized decalcification without areas of increased density





Polyostotic fibrous dysplasia (Albright's Syndrome). — A B C and D Woman who had normal menarche but 6 years ago *noted deformation of the face due to bony overgrowth Had 11 fractures* and café au lait pigmentation Serum calcium 10 mg % phosphorus 2 5 mg % phosphatase 10 Bodansky units Urinary calcium excretion low Exploration revealed no parathyroid anomaly X-rays show typical osteodystrophia fibrosa disseminata with cyst formation in numerous bones and great increase in skull density (Cont d on p 585)

(Courtesy of Dr A -B Ulhôa Cintra)

(7) Osteoporosis. The decalcification of the skeleton is generalized and of even intensity throughout. The condition occurs mainly in senile individuals, in Cushing's disease and in chronically bed-ridden patients as a result of disuse. Especially in children, marked bone atrophy, due to chronic disuse may be difficult to differentiate from hyperparathyroidism. Both conditions are accompanied by hypercalcemia, hypophosphatemia, hypercalcinuria, the occasional formation of renal calculi, anorexia, nausea and great muscular weakness. It must be remembered, however, that true primary hyperparathyroidism rarely (if ever) occurs in children and that in osteoporosis the cranium is not severely affected. Focal areas of decalcification with cyst formation speak decisively against osteoporosis.

(8) Other bone diseases. Gaucher's, Nieman-Pick's, Hand-Schüller-Christian's and Hodgkin's disease, osteogenesis imperfecta, osteomyelitis, the hemolytic anemias, erythroblastosis and polycythemia vera, have all occasionally been confused with hyperparathyroidism. If the possibility of these bone diseases is kept in mind, their characteristic manifestations usually permit a correct differential diagnosis

THERAPY

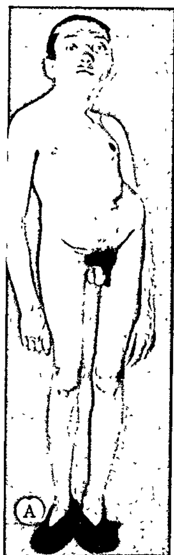
Operative Therapy. — In all types of primary hyperparathyroidism, the therapy of choice is surgical removal of the hyperfunctional parathyroid tissue. The causative parathyroid tumor is rarely of sufficient size to be directly detectable by palpation. In order to localize it, careful X-ray examination of the thorax and periesophageal region, with contrast meal, should precede the intervention If necessary, the operator should explore the entire region from the neck to the thymus, to find the hyperfunctional blastoma since only its complete removal can assure a permanent cure Removal of normal parathyroids is of no avail if — as is so often the case — the adenoma is situated in an ectopic gland.

In the event of diffuse hyperplasia of all four glands, secondary hyperparathyroidism must always be suspected. However, if diffuse hyperplasia is the primary cause of the disease, two or three glands may be removed. The prognosis in these cases is not as good as in those due to a single blastoma.

Only in rare cases of "circumscribed osteitis fibrosa," is there any indication



Hand-Schüller-Christian Syndrome. — A. 14-year-old boy with mild diabetes insipidus. Blood cholesterol 276 mg %, biopsy of skull shows typical xanthomatous lesion — B. Partial disappearance of bone lesion following X-ray therapy (Courtesy of Dr E.-P McCullagh)







Polyostotic fibrous dysplasia. — **A.** 30-year-old patient, height 5'3", weight 122 lbs Multiple brown spots (with smooth margins) over body Numerous fractures caused severe deformity Blood calcium 9 2 mg %, blood phosphorus 2 2 mg %, blood 'alkaline phosphatase' 4 2 Bodansky units Biopsy of parathyroids shows no abnormality — **B.** Widespread cyst formation involving ilia, femora and ischia There is no evident thinning of the right femur, while on the left, some deformity is associated with increased density medially, in the area of the lesser trochanter — **C.** Extreme deformation of the spine prevented the proper focusing for roentgenogram Such spinal deformities are seldom seen in hyperparathyroidism

(Courtesy of Dr E -P McCullagh)

TUMORS OF THE PARATHYROIDS

DEFINITION

In the parathyroids, as in many other endocrine glands, there are intermediate types between hyperplasias and true tumors. Pertinent instances are often referred to as nodular hyperplasias (See: p. 561.)

Only the epithelial tumors of the parathyroids are of endocrinologic importance because only they can produce hyperparathyroidism. The clinical syndrome, thus elicited, is essentially the same, irrespective of whether the glands are the site of simple hyperplasia, adenoma or carcinoma formation Hence, the endocrinologic manifestations of functional parathyroid tumors have been discussed conjointly with those due to hyperplasia (see: pages 561 and 571). In this section we shall deal only with tumors whose most salient characteristics are those of a true independent parathyroid neoplasm

It is well to bear in mind that primary parathyroid tumors never destroy all the parathyroids sufficiently to induce clinical hypoparathyroidism and that (for reasons which are still not understood) otherwise typical adenomas and mature carcinomas of the parathyroids sometimes fail to produce hyperparathyroidism

CLASSIFICATION

The tumors of the parathyroids may be conveniently classified as follows

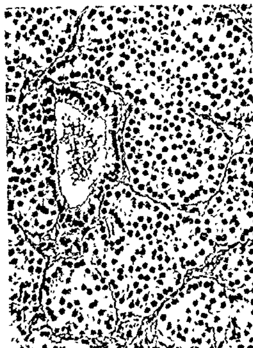
(A) Cysts
(B) Adenomas
(C) Carcinomas
(D) Mesenchymal Tumors

PATHOLOGIC ANATOMY

(A) Cysts. — Small cysts are quite frequently found even in the normal parathyroids. They are lined by an epithelium and contain colloid material. Sometimes, the entire parathyroid is transformed into a cystic mass, a phenomenon often described as "polycystic degeneration" Large primary cysts of the parathyroids are uncommon, although cystic degeneration of primarily solid tumors may occur.

(B) Adenomas. — These have been described in the chapter on Hyperparathyroidism and since their structure is essentially the same, irrespective of whether they do or do not cause hyperparathyroidism, it will not be necessary to reconsider them here

(C) Carcinomas. — Malignant epithelial tumors of the parathyroids have been described as "parastrumas," "malignant adenomas" or simply as parathyroid carcinomas They tend to be rather atypical and rarely produce signs of hyperparathyroidism. In some



Adenoma of the parathyroid. Typical adenoma of the parathyroids, which led to osteitis fibrosa Note small cyst in the central part of the field (Courtesy of Dr P Masson)

for bone resections The spontaneous fractures, on the other hand, may require local corrective surgical interventions if they heal in abnormal positions

Parathyroidectomy for scleroderma, marble bone disease, Raynaud's disease and thrombo-angiitis obliterans, are still in the experimental stage.

Pre- and Postoperative Therapy. — It must be kept in mind that the major danger in hyperparathyroidism, is not the decalcification of the skeleton but the metastatic calcium deposition in soft tissue, especially in the kidney (uremia) and heart (decompensation). Hence, it is inadvisable to administer calcium and phosphorus, PREOPERATIVELY in the hope of helping bone formation. In the presence of excess parathyroid hormone, such treatment is very likely to induce fatal soft tissue calcification.

Similarly, it is contraindicated to prescribe acidifying diets or acid-producing salts; these augment decalcification of the skeleton and enhance calcium excretion through the kidneys, hence, they may aggravate the renal lesions.

It is advisable, on the other hand, to force fluids in the hope of preventing the formation of renal calculi by diluting the urine.

POSTOPERATIVELY, a relative parathyroid hormone deficiency tends to develop in a large percentage of the cases. This is probably due to several reasons :

(1) The development of a sizable parathyroid adenoma causes compensatory atrophy of the remaining normal parathyroids.

(2) Hyperparathyroidism causes both bone absorption and new bone formation, but the newly formed bone is incompletely developed and consists of much organic material capable of taking up excess calcium. Mineralization of this excess new bone follows immediately, after removal of the source of excess parathyroid hormone. This process adds to the tendency towards hypocalcemia after the operation.

(3) Severe chronic hyperparathyroidism induces renal lesions which, in turn, call for excess parathyroid hormone secretion, comparable to that occurring in renal rickets and other types of secondary hyperparathyroidism.

(4) Following chronic exogenous overdosage with parathyroid hormone there is adaptation to the latter, so that discontinuation of the treatment is followed by hypocalcemia or even tetany. Removal of a parathyroid blastoma probably acts similarly to discontinuation of chronic treatment with parathyroid hormone injections.

Any or all of these etiologic factors may be responsible for the frequent development of hypocalcemia and tetany after ablation of a single blastomatous, hyperfunctional parathyroid. Fortunately, this hyperparathyroidism is usually transitory and may be prevented by pre- and postoperative administration of calcium, parathyroid hormone and vitamin D. For the reasons mentioned above, this therapy should be given for only a few days before the surgical intervention (danger of augmenting metastatic calcification). After the operation, the dosage may be gradually decreased, since the remaining parathyroid tissue soon undergoes compensatory hypertrophy, and the bones and kidneys revert to normal.

HYPERPARATHYROIDISM IN ANIMALS

Occasionally, parathyroid adenomas and "cystic degeneration" of the parathyroids occur in animals, especially in the horse.

In the fowl, secondary hyperparathyroidism is comparatively frequent due to lack of ultraviolet radiation, vitamin D or calcium in the diet

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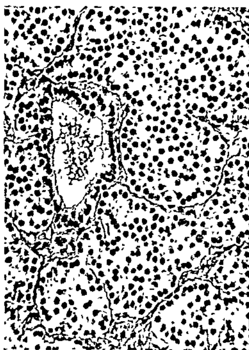
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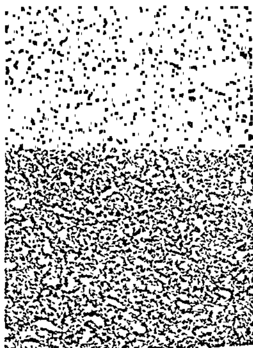
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Adenoma of the parathyroid. Typical adenoma of the parathyroids, which led to osteitis fibrosa Note small cyst in the central part of the field. (Courtesy of Dr P Masson)



Parathyroid carcinoma. Parathyroid carcinoma which led to hyperparathyroidism and marked hypercalcemia The section is taken from a recurrence (in the cervical musculature) after ablation of the neoplasm Note rather regular trabecular structure of the growth
(Courtesy of Dr P Masson)



Adenoma of the Parathyroid. Unusual adenoma of the parathyroid with osteitis fibrosa Note alveolar arrangement of cells, partly due to true follicle formation (similar to thyroid tissue) and partly to total liquefaction of the cells

instances, they develop in ectopic parathyroids.

Secondary, metastatic carcinomas of the parathyroids are quite exceptional

(D) Mesenchymal Tumors. — Angiomas, myomas, lipomas and "lymphomas" of the parathyroids have been described but all these tumors are exceedingly rare and of no endocrinologic significance.

CLINICAL COURSE

Cysts of the parathyroids as well as their mesenchymal tumors usually remain unrecognized and represent incidental findings at autopsy

The carcinomas follow a clinical course, similar to that of thyroid cancers and are characterized mainly by their local manifestations

By far the most important parathyroid neoplasms are the adenomas, most of which are functional and conducive to hyperparathyroidism, as described above (See : pp. 574-588.)

DIAGNOSIS

The diagnosis of the common functional tumors of the parathyroids is made on the basis of the hyperparathyroidism which they elicit. The endocrinologically "silent" neoplasms cannot be recognized as such Their local manifestations call attention to a tumor in the thyroid region and it is only following histologic examination of a biopsy or autopsy specimen that the true nature of this blastoma can be recognized

THERAPY

The therapy of any malignant parathyroid tumor should be surgical, although in inoperable cases, X-ray treatment may be attempted.

The majority of the "endocrinologically silent," benign parathyroid neoplasms require no therapeutic measures.

CONDITIONS INFLUENCING CALCIUM AND PHOSPHATE METABOLISM

CONDITION	Ca in Plasma	PO_4 in Plasma	Ca in Urine	PO_4 in Urine	Ca in Feces	PO_4 in Feces	Ca + PO_4 in Bones	"Metastatic Calcification"	Phosphatase in Plasma (alkaline)
Parathyroid deficiency	— — —	+	— —	—	On a high Ca low PO_4 diet: + On low Ca high PO_4 diet: N	+ N	— or N	N	N
Parathyroid hormone overdosage	+ + +	— — (in sublethal overdosage + + +)	+ + +	+ + +	N	N	— — — (after adaptation + + +)	+ + + (also renal calculi)	+ + ④
D—Avitaminosis (rickets & osteomalacia)	— or N	— or N	—	—	+ +	+ +	— — —	N	+ + +
D—Hyper vitaminosis	+ + +	+ +	+ + +		— —		— — — (after adaptation + +)	+ + +	
Renal insufficiency	— — — ①	+ + +	— —	—		+ + +	— —	N	+ + +
Metastatic bone tumors & Osteogenic sarcomas	+ +	+	+	+			— —	+	+ + ③
Hyperthyroidism	N	N	+ +		+		—	N	+
Hyperfolliculoidism	+						+	N	
Obstructive jaundice	—						—	N	+ +
High Ca, low PO_4 diet	+ +	—			+ + +				
Low Ca, high PO_4 diet	—	+ +				+ + +			
Sprue & celiac rickets	—	—	N		+ +	+ +	— — —	N	
Acidosis	+ or N	N		+ +	+ +	+ +	— — —	N	
Alkalosis	N ②	N	—					N	

\+ increase

— decrease

N no change (normal)

Space is left blank if pertinent data are not considered to be conclusive.

① reduction mainly due to fall of non ionized Ca (*hypoproteinemia*) *hence no tetany*. In advanced uremia hypercalcemia may occasionally develop, perhaps secondary to acidosis.

② decrease in diffusible, increase in non diffusible Ca

③ also high in Paget's disease, Gaucher's disease and generalized osteoporosis

④ both in osteitis fibrosa and marble bone disease

REFERENCES

ALBRIGHT, F., and E C REIFENSTEIN: *The Parathyroid Glands and Metabolic Bone Disease* Williams and Wilkins Co Publ., Baltimore (1948)

By far the best monograph on this subject (393 pages, 157 figures and tables, numerous references) Apart from skeletal changes caused by parathyroid dysfunction, the book contains many sections concerned with bone diseases produced by other metabolic derangements It is written in a very stimulating and highly competent manner by outstanding authorities in this field and contains numerous "Albrightian" diagrams which, as usual, are both amusing and instructive

CANTAROW, ABRAHAM AND MAX TRUMPER *Clinical Biochemistry* 3rd Ed, W B. Saunders Company, Philadelphia (1945).

A concise (647 pages) treatise concerning the main problems of clinical biochemistry. It is cited in this section because of its excellent description of biochemical changes in parathyroid diseases However, the reader will also find it most useful as regards data concerning metabolic disturbances in other endocrine disorders

CROTTI, ANDRÉ *Diseases of thyroid, parathyroids and thymus* 3rd Ed Lea & Febiger, Philadelphia (1938)

A beautifully presented profusely illustrated, treatise (1229 pages), part of which is devoted to the parathyroids. The author gives a fairly extensive review of the pertinent literature and describes many personal observations Chief emphasis is laid upon the clinical aspects of parathyroid malfunction

FISCHER-WASELS, B UND J BERBERICH *Epithelkorperchen und innere Sekretion* Handbuch der inneren Sekretion Eine umfassende Darstellung der Anatomie, Physiologie und Pathologie der Endokrinen Drusen Ed Max Hirsch 1, 432 (1932) Verlag von Curt Kabitzsch Leipzig (1932)

A brief but authoritative (40 pages) review of parathyroid pathology mainly from the morphologic point of view It contains a fairly extensive list of references (In German)

GUTMAN, ALEXANDER, B *Chapter VI. The Parathyroid Glands* Nelson New Loose-Leaf Medecine Ed, W W Herrick 3, 311 (1941) Thomas Nelson & Sons, New York

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HERXHEIMER, C.: *Epithelkorperchen* Henke und Lubarsch's Handbuch der Spez. Pathol Anat.u.Histol 8, 548 (1926). Verlag von J 'erlin (1926).

An extensive and most authoritative treatise concerning the pathologic anatomy of parathyroid diseases (In German)

KRAUS, E. J. *Nebennieren, Schilddrüse, Epithelkörperchen, Thymus, Zirbeldrüse und Inselapparat in ihren Beziehungen zur Frauenheilkunde.* Handbuch der Gynäkol S 580 u 69 Abb. B. 95, 324 (1936).

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MAMOU, HENRY. *Parathyroïdes.* Encyclopédie Médico-Chirurgicale, Glandes Endocrines. Maladies de la Nutrition 1st Ed, p. 10011 (1936)

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OKKELS, HARALD. *Les parathyroïdes (Actualités scient. et industr. Nr 307, Histophysiologie).* Hermann & Cie. Paris Publies par A. Policard I (1935)

A brief monograph mainly concerning the normal and abnormal morphology of the parathyroids. (In French)

PERITZ, G *Die Nebenschilddrüse.* Handbuch der inneren Sekretion Eine Umfassende Darstellung der Anatomie, Physiologie und Pathologie der Endokrinen Drusen Ed Max Hirsch 3, 959 (1928) Verlag von Curt Kabitzsch Leipzig (1928)

A brief (57 pages) review of parathyroid diseases with their theoretic evaluation The review of the literature is very incomplete (many references are incorrect), but the author mentions several interesting personal observations. (In German)

SNAPPER I *Medical Clinics on Bone Diseases. A Text and Atlas* Interscience Publishers, Inc, New York (1943)

A magnificently illustrated book (225 pages) a large section of which deals with parathyroid diseases The theoretic aspects of bone diseases are only briefly summarized The book is especially valuable as an atlas of bone diseases Main emphasis is laid upon X-ray diagnosis

VII

THE PINEAL

HISTORIC INTRODUCTION

Claudius Galenus, the famous Greek physician who worked in Rome (130-201 A.D.) described the pineal in his work "De usu partium." He considered it a secretory organ important in the process of thinking.

Subsequently, the French philosopher. *Descartes* (1596-1650) expressed the view that the pineal is the "seat of the soul," because of its central location within the brain *Magendie* (1795) assumed it to be a regulator of cerebral circulation.

Later naturalists considered the pineal to be a vestigial pineal eye, similar to that which in certain amphibians and reptiles remains well-developed throughout life. As with the earlier theories, this interpretation had to be abandoned.

Diseases. — In 1898, *Heubner* described a case of precocious sexual and somatic development in a 4½ year old boy, who, at autopsy, proved to have a teratoma of the pineal. By 1907, *Marburg* had collected 40 similar cases and outlined the syndrome of "macrogenitosomia praecox," which he ascribed to hypopinealism. However, when *Exner* and *Bose* (1900-1911) in animals, and *Dandy* (1915) in man, succeeded in removing the pineal, it became obvious that hypopinealism causes no detectable deficiency symptoms.

More recently, *Rowntree* et al. (1936) claimed that pineal extracts retard the growth rate, but accelerate sexual differentiation in rats, especially if treatment is continued through several successive generations. These observations have not been confirmed, and we may well say that to-day little more is known about the physiologic function of the pineal than in *Galen's* time. The only well established fact appears to be that tumors in, or around, the pineal are often associated with precocious sexual development and that the gland can be removed with impunity.

NORMAL MORPHOLOGY

ANATOMY

In man, the pineal body (corpus pineale, epiphysis cerebri, pineal gland, conarium) is a small, conical, reddish-grey structure situated in the depression between the superior colliculi of the quadrigeminal body. It is attached by a stalk to the roof of the third ventricle near the junction to the midbrain. It lies beneath the splenium of the corpus callosum from which it is separated by the tela chorioidea of the third ventricle, the lower layer of which envelops the pineal. The organ is about 8 mm long, and 3-5 mm thick at its base where it is broadest The stalk divides anteriorly into one ventral and one dorsal lamina, separated from each other by the pineal recess of the third ventricle. The ventral lamina is continuous with the posterior commissure, the dorsal lamina with the habenular commissure. The cavity of the third ventricle extends for a short distance into the pineal recess. (See p. 200.)

HISTOLOGY

The free surface of the pineal body is covered by the pia mater, the recess

by the ependyma of the third ventricle which continues directly into it.

CONNECTIVE TISSUE septa, containing many blood vessels, arise from the surface and penetrate into the organ, separating its parenchyme into CELL CORDS. The pineal consists of strands of epithelioid cells, with dark nuclei and a poorly-developed cytoplasm. These are surrounded by a fine reticular framework. In older individuals, the epithelioid cells gradually enlarge, acquire more cytoplasm and their nuclei become paler.

There has been a good deal of discussion concerning the identity of the various cell types within the pineal but most investigators agree that there are :

(1) Chief cells which are comparatively large and have small processes. Their homogeneous cytoplasm is free of vacuoles.

(2) Smaller cells with minute acidophilic granules

(3) Cells with basophilic granules.

(4) Cells with lipid granules

(5) Nerve cells.

(6) Neuroglia cells.

The presence of cell granules has been interpreted as an indication of incretory activity, especially since the *body has no excretory duct and hence* could not function as an exocrine gland.

In older individuals, so-called "BRAIN-SAND GRANULES" (acervulus, corpora arenacea) appear within the pineal parenchyme. These are inorganic concretions consisting mainly of calcium phosphates and carbonates with traces of magnesium. The appearance of these brain-sand granules is generally preceded by hyaline degeneration of the connective tissue septa and the parenchyme lobules. The VASCULAR SUPPLY of the pineal is derived from the tela chorioidea whose vessels are surrounded by LYMPHATIC channels and penetrate the capsule at several points.

The pineal body grows until about the 7th year of age, after which it begins to involute until the time of puberty.

COMPARATIVE MORPHOLOGY

Some equivalent of the pineal is present in all vertebrates. In fish, amphibia and reptiles, where the median parietal eye is particularly well developed, the pineal is comparatively inconspicuous, while in mammals which have no parietal eye, the pineal assumes greater proportions. For this reason, it has erroneously been thought that the pineal body was formed from the parietal eye in the course of phylogenetic development.

EMBRYOLOGY

In the human embryo, the pineal arises, at about the 7th week of prenatal life, from a fold on the roof of the diencephalon in the form of a nodule of round cells. By the end of the 6th month, these have become differentiated into typical neuroglia, nerve and pineal cells.

THEORIES CONCERNING THE HISTOPHYSIOLOGY OF THE PINEAL

Because of the epithelioid appearance and the granule content of the *pineal cells, they have generally* been regarded as having an endocrine function. This view appeared to be confirmed clinically by the frequent association of precocious sexual maturity with pineal tumors, and experimentally by the alleged morphologic changes in the pineal accompanying hormone deficiencies or over-dosage and pregnancy. The so-called typical "endocrine disturbances" following extirpation of the gland or the administration of pineal extracts, have also been cited as supporting evidence

Some authors have claimed that pinealectomy in the fowl results in precocious sexual maturity with enlargement of the accessory sex organs and testes; others believe that typical metab-

olic disturbances follow the administration of pineal extracts or pinealectomy. Recently it was reported that very young male (but not female) cats, dogs and rats show growth-acceleration after pinealectomy.

It was maintained, furthermore, that pineal extracts, administered daily to rats, over several generations, retard the rate of growth, while accelerating differentiation and especially sexual development Since the extracts used were rather impure, it is probable that the inhibition of growth was merely a toxic manifestation and not due to any specific hormone.

Most contemporary investigators agree that an endocrine function has not yet been definitely demonstrated by any of these experiments and that the pineal is probably a vestigial organ without significance in man; if it subserves a physiologic rôle, its nature is still unknown

DISEASES OF THE PINEAL BODY

Among the diseases of the pineal, only the tumors are of importance. These may be cholesteatomas, ganglioneuromas, teratomas or "pinealomas;" the latter consist of the typical histologic elements of the pineal Sometimes the term pinealoma is used to designate all pineal tumors, but this is confusing.

There does not appear to be any close relationship between the histologic structure of the pineal neoplasms and the clinical manifestations which they elicit. Hence, the various histologic types may be considered conjointly

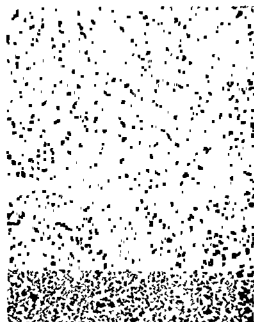
PATHOLOGIC ANATOMY

The cholesteatomas, ganglioneuromas and teratomas of the pineal region do not differ essentially from corresponding neoplasms found elsewhere in the body, so that we need not discuss them here.

The PINEALOMA consists of two cell types resembling the elements of the normal pineal. Some of the cells are large with voluminous vesicular nuclei, separated by a fine reticular stroma, while other cells resemble small lymphocytes. Because of this peculiar histologic structure, the pinealomas or "pineoblastomas" have often been described as carcinomas or sarcomas of the pineal.

INCIDENCE

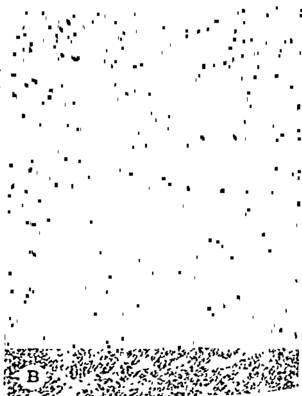
Pineal tumors are extremely rare and occur most frequently in males. They may develop at any age, but only in prepubertal children do they elicit manifest signs of sexual and somatic overdevelopment



Pinealoma. *Section through the pineal tumor of a 19-year-old man, with signs of intracranial pressure, but no genital anomaly Note diffuse arrangement of small epithelial cells, with abundantly developed stroma; the latter is heavily infiltrated by small round cells*

(Courtesy of Dr W P van Wagenen)

Pinealoma. — **A.** 41-year-old man, who suffered from loss of vision and hydrocephalus, but no genital anomalies At autopsy, a large tumor of the pineal was found to occlude the aqueduct of Sylvius, resulting in dilatation of the lateral and third ventricles



— B Trabecular histologic appearance of the above tumor (Courtesy of Dr W P van Wagenen)

PATHOGENESIS

The factors responsible for the development of pineal tumors are unknown although there is some reason to believe that most of them result from the neoplastic transformation of abnormal embryologic primordia in the pineal region.

The pathogenesis of the local manifestations need not be discussed since these are evidently due to compression or invasion of adjacent brain regions

The pathogenesis of the systemic (endocrine ?) manifestations of pineal tumors have led to a great deal of speculation and the following possibilities are to be considered·

(1) INTERNAL SECRETION BY THE TUMOR ITSELF. Since the most predominant manifestations of pineal tumors are premature, excessive sexual development *and* growth, it is tempting to postulate the existence of pineal hor-

mones which would elicit this clinical syndrome. We know that other endocrines (e g., adrenal cortex, pituitary, gonads) secrete substances which induce similar somatic changes.

It may be said against this hypothesis that the precocious development occurs with pineal tumors of varying histologic structure and irrespective of the presence of the so-called endocrine cells Furthermore, the same syndrome is even elicited by tumors causing complete destruction of the gland.

(2) INFLUENCE UPON THE HYPOPHYSIS It has been claimed that pineal tumors may produce clinical manifestations by compressing the hypophysis which lies caudad to them. Either stimulation or inhibition of pituitary functions has been postulated through this mechanism. Thus the pineal tumor could indirectly cause sexual development through gonadotrophic hormone, and somatic development through somatotrophic hormone overproduction by the adjacent pituitary. Since such manifestations rarely occur with pressure upon the pituitary due to other causes, these theories are meanwhile without solid foundation — It appears likely, however, that the obesity and diabetes insipidus, often associated with pineal tumors, are the result of mechanical interference with the function of the posterior-lobe or the hypothalamus.

(3) INTERFERENCE WITH THE BRAIN CENTERS. It has been suggested that the precocious development is due to compression or destruction of the infundibular hypothalamic centers, especially those regulating anterior-pituitary activity. This view was based upon the above-mentioned independence of the manifestations from the histologic nature of the blastoma and the fact that even tumors in the vicinity of the pineal, but not involving the latter directly, cause similar changes This is the most likely explanation of the pathogenesis of this syndrome at the present time.

CLINICAL COURSE

Perhaps the most striking manifestation of pineal tumors is the macrogenitosomia praecox or *Pellizzi's syndrome*, characterized by precocious sexual development and somatic growth. Even patients less than two years of age may begin to show signs of precocious differentiation as a result of such blastomas.

In children, the growth in length and the development of adult body-configuration and hair-distribution are strikingly precocious The sex organs assume adult size much before puberty and erections, emissions, masturbation, interest in women are among the typical manifestations of precocious sex-development.

Macrogenitosomia praecox appears to occur almost only in boys; pineal tumors in girls rarely elicit similar manifestations In adults of either sex, blastomas of the pineal likewise fail to elicit manifest sexual stimulation. On the contrary, in women there is usually amenorrhea, and in men testicular involution, presumably as a secondary result of the non-specific damage due to intracranial pressure It is not known why only some pineal tumors elicit signs of precocious puberty, but presumably this depends upon the particular brain centers affected by the growing neoplasm.

All other manifestations of pineal blastomas are probably directly due to the mechanical expansion of the growth with the resulting increase in intracranial pressure These manifestations are more or less diffuse or occipital headaches, vomiting, suboccipital tenderness, neck rigidity, muscular weakness and either hypo- or hyperthermia Among the ocular signs, the most striking are, progressive loss of vision (due to destruction of the optic chiasma and

tract), *and disturbances of eye movement and pupillary reactions* (due to compression of the lamina quadrigemina). Progressing intracranial pressure, deafness, loss of body weight, increasing stupor and drowsiness, sometimes accompanied by convulsions, tend to precede the fatal outcome. Invasion into the cerebellum may result in disturbances of muscular co-ordination and other cerebellar manifestations, while compression of the adjacent aqueduct of Sylvius causes internal hydrocephalus.

Mechanical interference with the *hypophyseo-hypothalamic functions* is probably responsible for the frequent occurrence of diabetes insipidus and adiposity in patients with pineal tumors. The blotchy pigmentation of the skin (rare), the often extraordinarily marked cachexia and the hypogonadism of adults have been ascribed to secondary anterior-pituitary failure.

COMPLICATIONS

The only complications likely to occur in the course of a growing pineal tumor are those due to the direct invasion or compression of the adjacent nerve centers. Since these form an essential part of the clinical syndrome, they have been discussed above under "Clinical Course."

DIAGNOSIS

Pineal tumors are frequently not recognized during life, chiefly because they are so rare that physicians fail to think of them.

In the presence of macrogenitosomia praecox, it is imperative to search for signs of an intracranial neoplasm, whose position may be determined by ventriculography and the neurologic signs, especially the ocular disturbances The latter manifestations may *aid in the diagnosis of these tumors even if there is no precocious development.*

From the differential diagnostic point of view, we must consider sexual precocity due to testicular and adrenocortical neoplasms, as well as true precocious puberty due to premature gonadal development. Since pineal macrogenitosomia *praecox* occurs only in the male, the cases of sexual precocity in girls can be eliminated, although it must be remembered that pineal tumors without sexual precocity may occur in females. Signs of *pseudohermaphroditism are not produced* by pineal neoplasms. The clinical manifestations of pinealomas may be exactly copied in every detail by growths in the adjacent regions of the brain which do not involve the pineal itself.

PROGNOSIS

When signs of intracranial pressure become obvious, *death usually ensues* within a few months to 2-3 years.

Repeated decompression of the brain combined with X-ray or radium treatment may prolong the life of the patient for several years and complete surgical removal of the neoplasm *may even* effect a permanent cure, but the postoperative survival rate is low.

THERAPY

Because of the above-mentioned high mortality of surgical operations, many brain specialists advise against any attempt to remove the neoplasm by a *radical intervention.*

Cerebral decompression, in combination with X-ray or radium therapy, is advisable as a palliative treatment, especially since some pineal tumors are rather radium-sensitive Permanent cures cannot be effected by such procedures.

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VIII

THE TESTIS

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HISTORIC INTRODUCTION

Morphology. — In 1677, *Anton van Leeuwenhoek*, the discoverer of the microscope, reported that using his primitive magnifying instrument, he was able to detect small "animalcules" in semen. This was the first description of human spermatozoa. *Dalentatius* (1699) and others believed that they had observed a minute human form in the spermatozoa and this gave rise to the so-called "preformation" theory, according to which the individual organs, though minute, are all present in the sperm cell. Not until 1759, was this fantastic claim effectively refuted by *Wolff*. *It will be recalled that* it was only in 1839 that *Schleiden* and *Schwann* showed the cell to be the structural unit of the organism and thereafter, ovum and spermatozoon were recognized as true cells. *Hertwig* (1875) was the first to observe and to understand the fundamental events of fertilization.

In 1850, the German anatomist, *Franz von Leydig* described the *interstitial cells of the testis which now bear* his name Shortly afterwards, the Italian histologist, *Enrico Sertoli* (1865) discovered the "footcells," to which the spermatids are attached during their development.

A few years later, *Marion G. Sims* (1867) — addressing the New York County Medical Society, on "The Microscope as an Aid in the Diagnosis and Treatment of Sterility" — emphasized the value of microscopic semen studies He complained bitterly that his work was impeded by incriminations that "this dabbling in the vagina with speculum and syringe was incompatible with decency and self-respect." The value of his procedure is now so generally accepted that he is *amply vindicated before posterity*. With "anti-vivisection" and "anti-drug" propaganda rampant even today, it is well to remember, however, how much medical research has had to suffer from prejudice and superstition ever since the ancient physicians were forced to rob graves in order to learn enough about the anatomy of the human body to help the sick.

Experimental Physiology. — The *earliest experiments on the endocrine* function of the testis were of such fundamental importance for the development of endocrinology as a whole, that we quoted them in the general historic introduction. After *Brown-Séquard's* rejuvenation experiments (1889), the Russian physiologist, *Pöhl* (1891) claimed that SPERMIN, an organic base contained in semen, is the active principle of the testicle. It is *noteworthy that although* this was entirely erroneous, industry began to manufacture spermin on a large scale and it was subsequently used in hypogonadism for many years, much to the satisfaction of physicians and patients alike This is another historic fact showing how readily false, subjective interpretations tend to be misleading, especially when they deal with sex-physiology

The first authentic clinical studies of male hypogonadism were published by the Viennese School *(Tandler and Grosz*, 1907-1910), on the basis of in-

vestigations made upon the Skoptsi, a religious sect, which, in Russia and Roumania, practised castration in young children. From their observations, the authors definitely concluded that the testes are not only concerned with reproduction, but in addition, exert important effects upon somatic growth, fat distribution and psychic development.

Also in Vienna, *Steinach* (1920) reported upon "rejuvenation" following resection of the ductus deferens; he ascribed this to reactivation of the endocrine functions of the testis. Almost at the same time, the Russian *Voronoff* (1923) claimed to have obtained rejuvenation, following transplantation of testes from man to man, or monkey to man. A few years later, *Doppler* (1931) asserted that periarterial sympathectomy on the spermatic vessels can reactivate the senile testis. None of these interventions withstood the test of time, but the great popularity which they enjoyed for several decades re-emphasizes the importance of rigorous objectivity in the interpretation of "rejuvenation" phenomena.

The first unquestionably potent TESTOID PREPARATION FROM BULL'S TESTES was prepared by alcoholic extraction at room temperature, by *McGee* (1927) in the United States. Shortly afterwards, highly purified testoid concentrates were obtained by *Dingemanse* et al. (1930) in Holland and *Frattini and Maino* (1930) in Italy This work was soon followed by the isolation of pure CRYSTALLINE TESTOSTERONE, also from bull's testes by *David* et al. (1935) in *Laqueur's* laboratory, in Amsterdam A study of these early publications clearly reveals that in this field, as in so many other branches of endocrinology, convenient bioassay methods played a decisive rôle.

Funk and Harrow (1930) succeeded in preparing TESTOID CONCENTRATES FROM THE URINE of men, but it soon became evident that most of the testosterone produced by the testis is excreted in the form of other metabolites, only some of which retain testoid potency. One of these, ANDROSTERONE, was first prepared from the urine of men, in Germany, by *Butenandt and Tscherning (1934)*.

Work on the metabolism of testoids has been greatly aided by the discovery of COLORIMETRIC REACTIONS (*Zimmermann*, 1935; *Callow et al.* 1938) suitable for the detection of neutral 17-ketosteroids or "17-KS" (the main excretion products of testosterone) irrespective of their physiologic activity

There was much argument concerning THE CELLS IN THE TESTIS WHICH PRODUCE THE TESTOID HORMONES. *Bouin and Ancel* (1903, 1923) were the first to ascribe the rôle of hormone production to the Leydig cells This view received strong experimental support by their observations showing that vaso-ligation and cryptorchidism, which destroy the seminiferous epithelium, but leave the Leydig cells intact, do not interfere with the endocrine activity of the testis. Later, the same was shown with X-ray treatment, exposure to heat and many other interventions. *Lipschutz and Wagner* (1922) pointed out that in spontaneously eunuchoid rabbits with atrophic accessory sex-organs, the Leydig cells are deficiently developed, while the seminiferous epithelium may remain normal The subsequent purification of FSH and LH, respectively, helped a great deal to clarify this point, since the former selectively stimulates the seminiferous epithelium, and causes no accessory sex organ development, while the latter stimulates the Leydig cells and simultaneously provokes manifestations of increased testis hormone secretion

Diseases of the Testis. — Unlike the diseases of the ovaries, those of the testes did not play a prominent rôle in the historic development of sex endocrinology

Apart from the very characteristic clinical consequences of TESTIS DESTRUCTION and their management by substitution therapy, the primary TUMORS OF THE LEYDIG CELLS were perhaps the most important. The first incontestable case of a Leydig cell tumor was described in the dissertation of *Chevassu* (1906). The most important pertinent morphologic questions have been clarified by the classic observations of *Pierre Masson* (1943), who also showed that concomitant with clinical signs of hypertestoidism, there is a greatly increased elimination of testoids in the urine.

The *first chorionepithelioma* of the testis was described in 1902 by *Schlagenhaufer*. The endocrinologic relationship between this tumor in the male and the placental chorionepithelioma of women was clearly demonstrated in 1930, almost simultaneously by *Zondek* and *Heidereich* et al., who detected enormous amounts of gonadotrophins in the urine of these male patients.

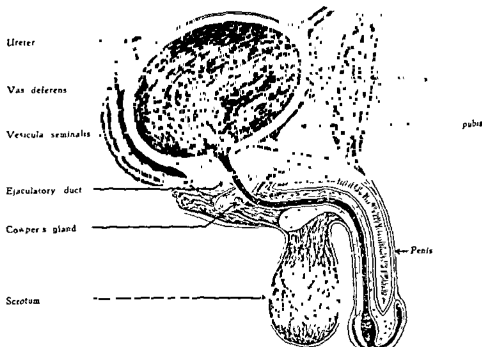
Comparatively recently, *Klinefelter* et al. (1942) described a "syndrome characterized by gynecomastia, a-spermatogenesis without a-leydigism and increased excretion of follicle-stimulating-hormone." This syndrome which revealed a number of interesting points concerning male sex endocrinology, is now generally known as "KLINEFELTER'S SYNDROME."

NORMAL MORPHOLOGY

ANATOMY

In man, the testes are paired, approximately egg or ellipsoid-shaped bodies, suspended in the scrotum. Their average MEASUREMENTS are about 4-5 cm in length, 2.5 cm in breadth and 3 cm. in the antero-posterior diameter. The total WEIGHT of the two glands is 21-28 gm. The epididymis is attached to the superior and posterior borders of the testis.

The free surface of the testis is covered by the visceral layer of the TUNICA VAGINALIS, a serous covering which



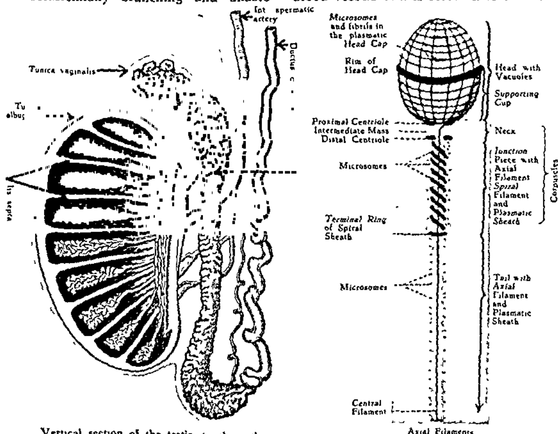
Vertical section of bladder, penis, and urethra
(Redrawn from H. Gray: The Anatomy of the Human Body. Lea & Febiger 1942)

forms part of the SACCUS VAGINALIS of the peritoneum. In the fetus the latter is continuous with the peritoneal mesothelium, but in the adult, it forms a separate pouch within the scrotum. Beneath this layer is the fibrous capsule of the testis, the TUNICA ALBUGINEA. At the posterior border of the testis, this capsule invades the gland, forming an incomplete vertical septum, the MEDIASTINUM TESTIS or corpus Highmori. From this mediastinum, thin connective tissue septa extend radially to the capsule, subdividing the testis into about 250-400 conical compartments, the LOBULI TESTIS. Each of these interseptal compartments contains 1-3 SEMINIFEROUS TUBULES measuring about 30-70 cm. in length and 150 to 250μ *in diameter. Their combined length in man amounts to about* 250 m They are highly convoluted, occasionnally branching and anastomosing with each other, or even (through holes in the septules) with seminiferous tubules in adjacent compartments.

Within the scrotum, the testes are suspended by the spermatic cords. These consist of blood vessels, nerves and the DUCTUS DEFERENS, the excretory duct through which the spermia, formed in the convoluted tubules, are eliminated. The EPIDIDYMIS is an elongated body, containing the first portions of the excretory duct system.

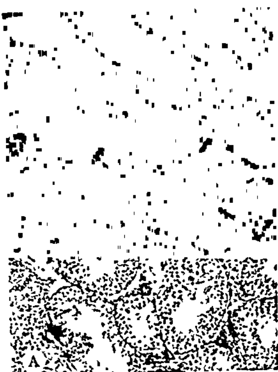
HISTOLOGY

The Capsule. — The tunica albuginea and the mediastinum consist of dense, collagenous, connective tissue. In the mediastinum, there are also a few smooth muscle fibers. Beneath the tunica albuginea is a layer of loose connective tissue, which contains many blood vessels and is referred to as the



Vertical section of the testis, to show the arrangement of the ducts
(Redrawn from H Gray The Anatomy of the Human Body Lea & Febiger 1942)

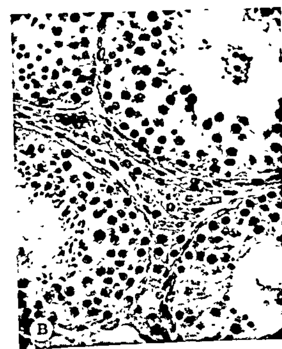
The "Neck" and "Junction Piece" are corpuscles as judged by electromicroscopic observations.
(After Joel, C A)

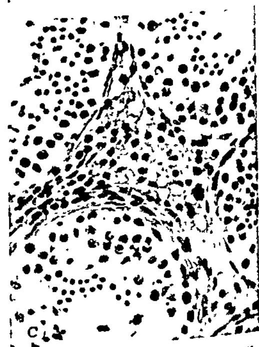


"tunica vasculosa testis." Prolongations of this layer continue inward along the septules, filling the angular spaces between the testicular lobules The covering mesothelium of the tunica vaginalis consists of flat, squamous cells, similar to those of the peritoneum.

The Seminiferous Tubules. — The postpubertal seminiferous tubule is lined by a stratified, rather complex type of epithelium, which rests on a thin, somewhat fibrillar, basement membrane, surrounded by laminated connective tissue. The seminiferous epithelium consists of two fundamentally different cell-types, the sustentacular or Sertoli cells and the germ cells.

The SERTOLI CELLS are large elongated and irregularly pyramidal elements, with their wide base attached to the basement membrane. They are placed at some distance from each other.





Normal testis (man). — A. Testis of an adult man Note various stages of spermatogenesis in tubular epithelium, Leydig cell clumps between the tubules, normal basement membrane delimiting tubules from stroma (Low magnification) — B. Higher magnification of a region from the above testis Note that among the tubules visible in this section, spermatogenesis (as judged by small dark sperm-heads on inner surface of lining) proceeds actively in some regions, but not in others The Leydig cells between the tubules are clearly visible, one of them forms a multinuclear giant cell — C. Higher magnification of another region of the above testis Note lymph accumulation (edema?) in the stroma This is quite common even in normal gonads In this region, spermatogenesis appears to proceed only to the spermatid stage (smallest round cells near inner surface of lining) The filamentous arrangement of the spirema in the primary spermatocytes is particularly obvious (Courtesy of Dr W Bonn)

around the circumference of the tubules. Between them are the various maturation stages of the germ cells. The outlines of the Sertoli cells are indistinct; their cytoplasm has a loose reticular structure and contains fibrils, basophilic and lipid granules, as well as small mitochrondria. In man, each Sertoli cell possesses a fusiform, crystalloid body near the nucleus. The cells are apparently phagocytic, since they engulf degenerated sperm cells, and the heads of the mature spermia are temporarily embedded in the apex of the Sertoli cell pyramids before their ejection into the lumen (see below).

The vesicular Sertoli cell nucleus is oval, it includes a large nucleolus and measures about 9 $\times$ 12μ, the longer axis being radially oriented within the tubule.

The SPERMATOGENIC OR GERM CELLS — like *the corresponding cells of the* female —undergo a complex process of maturation before they are ready for fertilization.

In the first phase (spermatocytogenesis), the youngest cells, the SPERMATOGONIA, mitotically divide several times (period of proliferation). During this phase, they retain their position along the inner surface of the basement membrane and do not noticeably change their histologic structure.

Subsequently each spermatogonium increases in size (period of growth) forming the somewhat more centrally located *primary spermatocytes*. These are also roundish cells, but both their nucleus and their cytoplasm are larger than those of the spermatogonia

Every primary spermatocyte divides into two new cells (period of maturation) the *secondary spermatocytes*, each of these soon divides again, forming two *spermatids*. The round shape of the cell is preserved during these last mentioned two divisions, but the secondary spermatocytes are somewhat smaller than the primary, while the spermatids are the smallest and most centrally located spermatogenic elements. It is during this last division that the chromosome number is halved ("haploid" or miotic division).

The mature male germ cells are the *spermia* (or spermatozoa), which arise from the spermatids without further division by transformation of their cell body into a shape specific for the different species, and differing from all other cells of the body.

The spermatogonium, like any other somatic cell, contains 48 *chromosomes* in man, but two of them, the so-called heterochromosomes, or sex chromosomes (X + Y), are different in shape and are *the* determinants of the offspring's sex. During the first miotic division these two heterochromosomes separate, so that each of the resulting daughter cells contains either an X or a Y chromosome, in addition to 23 of *the ordinary somatic chromosomes*. The spermatids, which result from the division of these secondary spermatocytes, have essentially the same chromosomal constitution. Hence, half of the resulting spermia (which are formed merely through a change in the shape of the spermatids) contains the X, the other half, the Y heterochromosome Since all the mature egg cells contain only X chromosomes (carriers of the female constitution), the sex of the offspring will be female, if the ovum is fertilized by an X-chromosome-containing sperm cell and male if inseminated by one containing a Y chromosome. As stated in connection with the maturation of ova (see: p. 328), the sex of the offspring is exclusively determined by *the male gamete*

The mature human spermium consists of an almond-shaped head, 4-5μ in length and 2 5-3 5μ in width. This is a transformed nucleus. Attached to one pole of the head is the middle-piece or neck, a rod-shaped portion about 5μ in length and 1μ in thickness. This part connects the head with the tail, which is about 52μ long and of gradually de-

creasing thickness. It is not possible to differentiate between the X- and Y-chromosome containing human spermia, since their histologic structure is identical in mature cells in which the chromosomes are part of the nucleus.

Abnormally shaped spermia (with two heads, two tails, malformed necks, etc.) are quite common in man and extensive degenerative changes among the spermia may cause sterility and perhaps even malformations among the offspring. A detailed description of the extremely complex structure of the spermia is not within the scope of this book.

It is believed that the fully mature spermia (which have no cytoplasm) are temporarily enclosed in the tips of the Sertoli cells for protection and nutrition. They are discharged into the lumen of the seminiferous tubules, when ready for fertilization. Although in man, spermatogenesis proceeds throughout reproductive life, independently of the seasons, the waves of spermatogenesis are not synchronous in the different tubules of the same testis. Thus some tubules may contain numerous spermia at a time when others are filled mainly with less advanced stages in spermatogenesis.

The terms SEMEN or SPERM should not be used for the spermatozoa or spermia themselves, but for the ejaculate, which, in addition to the spermatozoa, contains the secretions of the accessory sex glands. The normal ejaculate of man contains 180-360 million spermia.

The Stroma. — Apart from the collagenous septules between the lobules, the stroma consists of loose, reticular connective tissue, containing blood and lymph vessels, nerves, fibroblasts, mast cells, fixed macrophages, and the INTERSTITIAL CELLS OF LEYDIG. The latter are of special importance, because they produce the testoid hormones. They tend to form small nests which fill the angular spaces between the tubules.

The Leydig cells have a diameter of 14-21μ and an irregularly polyhedral cytoplasm. The latter contains numerous mitochondria and lipid granules, a pigment known as lipofuscin, and rod-shaped crystalloids with pointed or rounded ends, the so-called "Reinke crystalloids." The nucleus is large, spherical or wrinkled, containing coarse chromatin granules and one or two nucleoli. Giant Leydig-cells with two or three nuclei are fairly common and conversely, atrophic interstitial cells, which resemble spindle-shaped fibroblasts, occur in comparatively inactive testes.

The so-called SYMPATHICOTROPIC CELLS of the testis are sub-capsular Leydig cells attached to, or enclosed in nerves.

The testicular ARTERIES are derived mainly from the internal spermatic artery. They enter the gland through the mediastinum and either penetrate directly into the interior or course for some distance under the albuginea in the tunica vasculosa. A loose network of capillaries and sinuses is seen between the tubules and around the Leydig cells. The tubular epithelium has no vessels.

LYMPHATIC CAPILLARIES are demonstrable between the seminiferous tubules, and the larger lymph vessels lead through the mediastinum testis.

The testicular NERVES arise from the internal spermatic plexus and form microscopic periarterial plexuses within the organ.

The Duct System. — At the tip of each lobule, its seminiferous tubules join and continue into the TUBULI RECTI. These are short, straight, rod-like structures, having a diameter of 20-25μ and lined by Sertoli cells. They connect the seminiferous tubules with the rete testis in the mediastinum. The RETE TUBULES form an anastomosing reticulum, lined by cuboidal or squamous epithelial cells with a central flagellum

From the posterior border of the mediastinum, 12-14 or even more DUCTULI EFFERENTES arise. They are about 4-6 cm. in length and 0.6 mm. in diameter. Through many convolutions, they connect the rete with the main duct of the epididymis. They are lined by a rather complex epithelium with mobile cilia and so-called intra-epithelial glands.

The DUCTUS EPIDIDYMIDIS is a highly convoluted 4-6 m. long duct, lined by a pseudostratified columnar epithelium, whose surface carries non-motile stereocilia. This duct gradually straightens and continues into the 40-45 cm. long DUCTUS DEFERENS or vas deferens. The epithelium of the latter is essentially the same as that of the ductus epididymidis, but it has a much more developed, rather muscular, wall.

COMPARATIVE MORPHOLOGY

The spermatozoa show an extraordinary variety of shape and size in the different animal species.

Leydig cells appear in cyclostomata (e.g., myxine glutinosa) and exist in all higher stages of the evolutionary scale from fish to man.

In certain TOADS there is a vestigial ovary-like structure, Bidder's organ, in the vicinity of the testis It hypertrophies after castration

It has been claimed that the Leydig cells in the testes of so-called "hen feathered" breeds of FOWL (e.g., Sea-bright bantam), resemble corpus-luteum cells and that they differ essentially from the Leydig cells of other breeds, in which the cock has the male type of plumage. Re-examination proved, however, that special "luteal-cells" do not exist in hen-feathered breeds, so that there is no detectable morphologic basis for the anomaly in the hormone production which is responsible for their peculiar plumage

The existence of Leydig-cell-like elements in the epididymis of certain MAMMALS (e.g., dog) has been held responsible for the occasional persistence of male characteristics after castration Leydig cells of the "hilus cell" type, similar to the hilus cells of the ovary, are frequently seen in the mediastinal and subcapsular regions of the testis, where they tend to develop in close contact with nerves. It must be kept in mind, however, that accessory adrenal-cortical tissue, which greatly resembles Leydig cells, occurs quite frequently in the epididymis and spermatic cord region.

For the seasonal variations in the testicular structure of species with limited breeding periods see "Stimuli Influencing Testis Structure" (p. 641).

EMBRYOLOGY

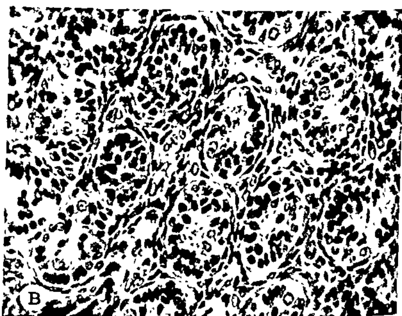
The development of the early, undifferentiated gonad has been discussed in connection with the embryology of the ovary. In man, the testis begins to show distinguishing characteristics in 13 mm. embryos. At this time, branched and anastomosing testis-cords appear and a tunica albuginea develops between these and the covering epithelium. The testis cords consist chiefly of undifferentiated cells, with only a few large germ cells between them. At about the second month, the originally compact cords begin to show a lumen, but this process of canalization is not complete, even at birth.

The interstitial cells appear first in the 19.5 mm. human embryo probably arising from mesenchymal cells or from the sex cords themselves. They are abundant at birth, but subsequently vanish, reappearing in full activity at the time of puberty Spermatogenesis commences at this same time

It will be recalled that the seminiferous tubules are formed from the first proliferation of the germinal epithelium and correspond to the medullary cords in the embryonic ovary. In the male, there is no second proliferation of the germinal epithelium, corresponding to



Testis of newborn (Man). — A. Note solid structure of immature gonad, in which the tubules are not yet canalized



— B. Higher magnification of the same section Note absence of lumina in the tubules which contain only earliest stages of spermatogenesis The stroma consists mainly of connective tissue, although some Leydig cells have already become differentiated

(Courtesy of Dr W Bonin)

that which creates the cortex of the ovary.

Many embryologists believe that the primitive sex-cells, which come to the gonad from the caudal end of the embryo, eventually degenerate both in the male and female and that the definite germ cells develop secondarily from the invading germinal epithelium in either sex. In lower invertebrates (e g , ascaris), the sex cells are separated from the somatic cells at a very early stage of development and the definite sex cells are undoubtedly derived from the primary In vertebrates, the demonstration of such a direct continuity in development is much more difficult. — Certain investigators claim that the definite sex cells, which develop from the germinal epithelium, are actually formed from temporarily "dedifferentiated" primary sex cells, which are neverthe-

less direct derivatives of the primordial gametes. It is not within the scope of this book to enter into the complex arguments concerning this much disputed embryologic question.

THEORIES CONCERNING THE HISTOPHYSIOLOGY OF THE TESTIS

Interrelations between the Various Cell Types. — Some of the pertinent points have already been discussed above (see: Embryology). The early theories according to which the Leydig cells are merely specialized types of histiocytes, or fibroblasts, or Sertoli cells which secondarily migrate into the stroma, have not received confirmation. It is most probable that these elements arise by direct metaplasia from the embryonic mesenchyme or from the undifferentiated epithelial cells of the sexual cords.

The Pathways of Testis Hormone Secretion. — Morphologic studies in animal species which exhibit a seasonal estrus, led to the assumption that, during the off-season, the Leydig cells accumulate "nutritive material," subsequently used by the spermatogenic epithelium, for the production of sperma during the breeding season. Some such trophic rôle is also suggested by the observations that injected testoids and Δ^5-pregnenolone — that is, hormones presumably produced by the Leydig cells — maintain the spermatogenic epithelium in hypophysectomized animals.

On the other hand, it has been claimed that the pathway of secretion is in the opposite direction and that the tubular cells produce precursors of testoids, which are transferred into the Leydig cells before the finished hormone is discharged into the blood-capillaries. It is not known, as yet, whether there is any direct exchange of hormones or hormone precursors between the Leydig cells and the tubular epithelium, but the testoids can exert a trophic influence upon the tubules when they reach them through the blood stream. (See: pp. 58, 64, 73, 630 and 638.)

Which Cell Produces the Testis Hormone? — The SPERMATOGENIC EPITHELIUM has often been regarded as the sole source of testis hormone. Champy emphasized that in the mole, the interstitial cells are best developed during the off-season and hence, cannot be made responsible for male hormone production. Others (e.g., Courrier) pointed out, however, that in most mammals with a seasonal estrus, the interstitial cell and accessory-sex-organ development run parallel. Besides, usually the increase in interstitial tissue during the off-season is only apparent, being due to the proportionally smaller space taken up by the atrophic tubules. In any event, a lack of parallelism between one of the testicular components and the accessory sex organs proves little with regard to the origin of the testis hormone. Excessive development of a certain cell type during one season may equally well be due to hormone storage or increased hormone production.

Another much used argument against the Leydig cells as hormone-producers was the erroneous belief of early investigators that such cells are absent in fish.

It has been claimed that the growth of the capon's comb can be stimulated by injection of spermia collected from the epididymis, but this has not been confirmed. In any event, this would not exclude the possibility that the testoids are secreted into the tubular lumina by the Leydig cells and enter secondarily into the sperm.

The bulk of evidence indicates that the LEYDIG CELLS are the testoid producers (Bouin and Ancel). In spontaneously eunuchoid rabbits, with atrophic accessory sex organs, the Leydig cells are deficiently developed, although the seminiferous epithelium remains functional (Lipschutz). Con-

versely, after vasoligation, X-ray treatment, exposure to heat or artificial cryptorchidism, the seminiferous epithelium degenerates, while the Leydig cells remain well preserved and the accessory sex organs show no signs of testoid hormone deficiency.

Experiments on hypophysectomized rats indicate that treatment with LH stimulates the Leydig cells, without significantly interfering with the disintegration of the spermatogenic epithelium. In such animals, the accessory sex organs show excessive development, indicating a greatly augmented testoid production.

While tumors of the spermatogenic epithelium are not accompanied by signs of excessive male hormone production, Leydig cell tumors (both in men and in women) cause pronounced signs of hypertestoidism which disappear following successful ablation of the neoplasms. This is additional evidence in favour of the Leydig cell theory.

Some workers claim that both the TUBULAR EPITHELIUM and the LEYDIG CELLS are in some way involved in the biogenesis of the testoids. This view has already been mentioned in connection with the pathways of testis hormone secretion. While there is some reason to believe that the tubular elements and the Leydig cells may exert *trophic influences upon each other*, contemporary opinion is greatly in favor of considering the Leydig cells as the testoid producers.

CHEMISTRY OF THE TESTIS

CHEMICAL COMPOSITION OF THE GLAND

The chemistry and biogenesis of the testicular hormones will be discussed in subsequent chapters. Here, we shall *merely consider the most important* facts concerning the general chemical composition of the gland.

The testes — like most tissues — contain only about 20% SOLIDS, the rest is water.

The CARBOHYDRATE content of the testis is low and mainly due to traces of glycogen

LIPIDS are stored almost exclusively in the Leydig cells, which are nearly as rich in fatty substances as the adrenal cortex or the corpus luteum. Since the *Leydig cells represent only a small portion* of the total testicular mass, the mean lipid content of the testis is much lower than that of the adrenal or ovary The principal fatty substances of the testis are fatty-acids, cholesterol, cholesterol esters, phosphatides and lipochromes. The latter are responsible for the yellowish color of testis tissue in which the Leydig cells are predominant (e.g., cryptorchid testes, Leydig cell tumors).

PROTEINS represent by far the most important component of the dry material in testis tissue.

As in most other organs, *the principal* INORGANIC CONSTITUENTS of the testis are sodium, chlorides, potassium and phosphates. However, zinc, bromide, sulphur, copper, calcium and iron have also been demonstrated.

Among the ENZYMES of the testis, hyaluronidase ("spreading factor" of Duran-Reynals) appears to play an important rôle. It is present not only in the testis itself but also in the ejaculate, and there appears to be a close relationship between the spermatozoon and hyaluronidase content of the latter. This enzyme has mucolytic properties and is probably important in dissolving the corona radiata cells around the ovum, thus exposing the egg to penetration by the spermium Various proteases, lipases, phosphatases, arginase and β-glucosaminase have also been found in testis tissue.

Little is known about the functional significance of other constituents of the male gonad (e.g., glutathione, choline, acetylcholine).

CHEMISTRY OF THE TESTIS HORMONES

The principal testoid hormone of the testis is testosterone, although other hormonally active principles (e.g., folliculoids, Δ^5-pregnenolone and perhaps, even some odoriferous steroid substances) are also present in it. All known testicular hormones are steroids and their fundamental chemical characteristics have been described in the section: The Steroids.

GENERAL PHARMACOLOGY OF THE TESTIS HORMONES

STANDARDIZATION

The direct gravimetric determination of testoids can only rarely be employed, because of the minute quantities present in body fluids and tissues. The most commonly used methods are based upon colorimetric and biologic determinations *of varying degrees of specificity and* accuracy. In general these can be performed on partially purified extracts containing testoids or their metabolites.

The available analytic methods are neither specific nor accurate enough to permit the exact determination of testoids in biologic material. They do not differentiate the biologically active from the inactive metabolites of similar structure and they fail to detect advanced degradation products (e.g., those in which the steroid nucleus is destroyed).

It must be realized, furthermore, that testosterone is not excreted as such and all of its metabolites are less active than the hormone itself, some of them being even completely inactive. Hence, urinary bioassays can only give an approximate estimate of the endogenous testosterone production.

Analytic Methods for the Detection of Testoids. — The most commonly employed analytic methods are COLORIMETRIC. The fundamental principles upon which these tests are based have already been mentioned in connection with the colorimetric estimation of the chemically related folliculoids. *Zimmerman* (1935) found that substances with an active methylene group, especially — $CO\text{-}CH_2$ —, produce a red color in the presence of alkali and meta-dinitrobenzene. Such a grouping is not only present for instance in ring D of androsterone, etiocholane-3(*a*)-ol-17-one, and other testosterone metabolites, but also in estrone. However, the *various modifications* of this test differentiate between ketonic testoid and ketonic folliculoid derivatives since it is possible to separate the phenolic from the non-phenolic 17-KS (*Oesting* and *Webster*, 1938; *Callow et al.* 1938). The acid phenolic 17-KS can be removed by washing with alkali and the remaining neutral 17-KS represent primarily degradation products of testosterone. Yet the specificity of the colorimetric 17-KS determinations is not very great and the results obtained with them are of value only when taken in conjunction with other laboratory and clinical findings.

Bioassay of Testoids. — The INTERNATIONAL UNIT (I.U.) of testoid activity is, by definition, that equivalent to the testoid potency of 100γ of pure androsterone tested under the same bioassay conditions.

The most commonly used testoid assays are the following:

(1) In the ORDINARY CAPON'S COMB TESTS (*Funk* et al. 1929, *Tschopp*, 1935), adult capons receive the compound to be assayed by intramuscular (pectoral) injection in oil solution. It is customary to express the results in *capon units* (C.U.), which are equivalent to the total amount of a testoid

versely, after vasoligation, *X-ray treatment*, exposure to heat or artificial cryptorchidism, the seminiferous epithelium degenerates, while the Leydig cells remain well preserved and the accessory sex organs show no signs of testoid hormone deficiency.

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potency, which enables this steroid to maintain spermatogenesis in hypophysectomized or folliculoid-overdosed animals.

Among the active testoids, we distinguish two main groups, exemplified by testosterone and androsterone respectively. The testosterone-type compounds are especially potent in stimulating the seminal vesicles and the capon's comb, while the androsterone-type substances prove comparatively more potent in stimulating the prostate. It is noteworthy that all testoids also exhibit a certain degree of folliculoid and anesthetic potency and that many compounds of this group have fairly marked luteoid properties.

The artificial testoids prepared to date are all derivatives of the natural steroid compounds. Among them, methyl-testosterone is especially noteworthy because of its high oral activity. Most other testoids are comparatively inactive when taken by mouth. The testosterone esters, especially the propionate, have the advantage over the free compound that their action is more prolonged, due to delayed absorption. Ethynyl-testosterone (see . "The Ovary") is an orally active luteoid with slight testoid potency.

When tested by subcutaneous injection in the rat, testosterone and methyl-testosterone are approximately equally active (I.U. = 15γ), while androsterone is considerably less active (by definition, I U. = 100γ)

MODE OF ADMINISTRATION AND CHIEF INDICATIONS

Testosterone and its esters are highly effective when given by INTRAMUSCULAR OR SUBCUTANEOUS INJECTION, in clinical medicine the former is generally preferred. Testosterone propionate is usually distributed in ampules containing 5, 10 or 25 mg. in 1 cc. of oil. In various types of male hypogonadism (eunuchism, eunuchoidism, impotence, male climacteric). 10-25 mg. given intramuscularly 3 times a week is most commonly recommended. The lower dose levels are preferred for the treatment of the male climacteric. In the treatment of benign prostatic hypertrophy favourable results are sometimes obtained using 5-25 mg. of testosterone propionate 3 times a week. This treatment was introduced because prostatic hypertrophy tends to develop when normal testicular function begins to fail, but the rationale of this therapy is not clear.

In women suffering from functional uterine bleeding, functional dysmenorrhea, endometriosis or cystic hyperplasia of the breast, 10-25 mg. of testosterone propionate, 3 times weekly, has been recommended, but some gynecologists strongly oppose the use of testoids in women under any conditions. For the suppression of lactation and for climacteric disturbances in women, the use of testoids is certainly unjustified, since folliculoids are even more effective and do not cause virilization.

Among other, less generally accepted, but suggested indications for the use of testoids, we might mention: scleroderma, malignant hypertension, angina pectoris and other cardiovascular diseases, as well as chronic emaciation, convalescence and dwarfism, in which the nitrogen-retaining, renotrophic and growth-promoting effects of the testoids are sought.

For ORAL USE, methyl-testosterone is given, usually in the form of tablets containing 10 mg. The indications are the same as for testosterone propionate, but the dosage should be at least 4 times higher These tablets are usually given daily, since continuous administration is more effective and the inconvenience of injections is avoided with this compound in any case.

It is still not quite clear to what extent the oral activity of methyl-testosterone is due to decreased destruction

which, given in 6 consecutive daily injections, yields a 20% average increase in the weight or area of the capon's comb. An *international capon unit* (I.C.U.) has been defined as equivalent to the testoid action of 200γ of crystalline androsterone, but it is rarely employed.

(2) In the CAPON'S COMB TEST WITH TOPICAL APPLICATION (*Fussganger*, 1934; *Dessau*, 1935), the extract to be assayed is administered (in oil or propylene glycol), by direct inunction to the capon's comb, daily for four days. The unit is the amount which elicits the same response as 0.7γ of androsterone.

(3) The CHICK COMB TEST (*Frank et al.* 1942) uses 2 to 3 day old single-combed white Leghorn chicks, which receive the testoid material in 7 daily topical applications to the comb. Active rubbing or inunction is avoided to eliminate possible mechanical stimulation of the comb growth. The material to be assayed is dissolved in 10 cc. of oil, of which 0.05 cc is lightly spread over the entire comb surface of each chick every day. The comb size is estimated by weighing after excision. The activity is calculated in reference to a chart in which the effect of standard doses of testoids are listed

(4) There are various TESTS BASED UPON THE STIMULATION OF THE SEMINAL VESICLES, PROSTATE AND PREPUTIAL GLANDS (*Martins* and *Rocha e Silva*, 1929; *Loewe* and *Voss*, 1929, *Moore* and *Gallagher*, 1930) of castrate adult or prepubertal rats or mice. Various rat and mouse units have been proposed, depending upon the weight increase or histologic signs of stimulation, which are regarded as criteria of activity. For most purposes it is better, however, to express results in I.U., using androsterone as a reference standard.

(5) The SWORDFISH TEST (*Binet* and *Luxembourg*, 1939) takes advantage of the fact that the development of the masculine "sword" in female specimens of *Xiphophorus Helleri* is readily elicited by testoids injected into the fish or added to the water in which they live. This test has not yet received much attention, although it appears to be very sensitive.

(6) The CLASPING-REFLEX TEST (*Steinach*, 1910; *McCartney*, 1929) estimates testoid activity by the ability to restore the copulatory reflex in frogs after orchidectomy, or during the winter season when it is normally absent. This test is rather inaccurate and mainly of historic interest.

Numerous other bioassay technics for testoids are based upon the ability of these compounds to restore EJACULATION, to promote the growth of the EPIDERMAL THORNS OF THE PENIS, or to maintain the MOTILITY OF SPERMATOZOA in the epididymis of the guinea pig after castration etc., but none of these enjoy great popularity.

PHARMACOLOGY OF TESTIS HORMONE DERIVATIVES AND ARTIFICIAL TESTOIDS

The general pharmacology of the testoids is discussed in the section: "The Steroids," and their specific actions on individual target organs in the chapter "Experimental Physiology of the Testis"

Suffice it to recall here that testosterone, which is presumably the natural testoid hormone, exhibits all the characteristics of the testoids. Androsterone, *iso*-androsterone, dehydro-*iso*-androsterone are considerably less active, while etiocholanolone and several other testosterone metabolites are entirely devoid of testoid potency.

Δ^5-pregnenolone is probably also a testis hormone, since it has been isolated from the testis and it exhibits hormone-like properties; yet this compound is devoid of testoid activity. It possesses a slight prostate-stimulating effect (which is "potentially independent" of the testoid action), but its main property is its strong spermatogenic

EXPERIMENTAL PHYSIOLOGY OF THE TESTIS

EXPLANTATION OF THE TESTES

Testis tissue grows quite well in TISSUE CULTURE. In suitable media, both the tubular elements and the Leydig cells can be maintained, for days or even weeks, in vitro; it has been claimed that the addition of anterior lobe fragments to such tissue cultures directly stimulates both the tubular and interstitial cell elements.

The testicular cells of immature or embryonic animals grow better than those of adults; in general, the lower the position of an animal in the evolutionary scale, the better are the chances of obtaining successful tissue cultures from its organs. Nevertheless, even adult mammalian testis can be grown in vitro on artificial media.

Of all the constituents of the male gonad, the mature spermatozoa are best suited for life outside the body, a quality which is essential, of course, for the process of insemination. They remain viable and motile for many hours in the ejaculate and they can be preserved in comparatively simple media (even in ordinary physiologic saline solution). For this reason, suspensions of spermia are frequently used for the study of metabolic processes under in vitro conditions The comparatively rapid death of spermia after mating, is due specifically to noxious actions exerted by the female genital secretions upon male gametes which have not penetrated the ova

The ORGAN CULTURES of whole testes, or of large testis fragments, has also been successful. Thus, testes of rats, guinea pigs, cats and rabbits have been maintained for 4 or 5 days by perfusion through their blood vessels with suitable fluid media, according to the Carrel-Lindbergh technic or one of its modifications. Sometimes, polynuclear giant cells (a sign of degeneration) are formed from the tubular elements, but often both the spermatogenic and the interstitial tissue remain essentially normal. Active proliferation of these tissues has not yet been clearly demonstrated, under such conditions.

It is evident that the in vitro culture of organs has great possibilities since this technic permits the study of factors influencing endocrine secretion and spermatogenesis under less complicated conditions than those prevailing within the organism. This type of experimentation may be able to tell us, among other things, from what raw materials and under the influence of what nervous and hormonal factors the formation of gametes and hormones is accomplished by the testis.

TRANSPLANTATION OF THE TESTES

As with other endocrine glands, the AUTOPLASTIC TRANSPLANTATION of the testis gives the greatest chance for survival; HOMOTRANSPLANTS are less likely to be successful, while HETEROTRANSPLANTS have never been consistently successful in higher vertebrates.

It has been claimed that even in man, homotransplantation of thin testis-tissue slices is sometimes successful. However, prolonged survival of such grafts has never been clearly demonstrated and reports of successful grafting of animal testes (e.g., those of apes or monkeys) into man, are even less convincing

It is also important to bear in mind, in connection with such grafts, that mammalian testis tissue requires a comparatively LOW SURROUNDING TEMPERATURE for the successful growth and proliferation of seminiferous cells. This is probably one reason why in amphibia and birds (whose testes are normally within the celomic cavity), transplantation of testis tissue is usually successful in any location, while in mammals, similar grafts rarely take, and never

(in the intestinal tract, the liver and other tissues), or merely to delayed and hence more efficacious absorption from the gastrointestinal tract. The latter factor seems to be more important, since orally administered testosterone is rapidly excreted in the urine in the form of 17-KS compounds. Unlike cholesterol and many other steroids with long side-chains, testosterone (and other short side-chain steroid hormones) are readily absorbed from the gastrointestinal tract, even in the absence of bile. This was demonstrated in animals whose bile duct had been tied.

Subcutaneous implantation of CRYSTAL PELLETS or SUSPENSIONS is recommended, especially for the treatment of chronic hypogonadism. 100-200 mg. pellets of methyl-testosterone can be implanted through a large-bore needle and remain effective for about two months, thus saving the patient the inconvenience of continuous treatment.

SUBLINGUAL administration of testosterone and its derivatives is likewise effective, but since the introduction of the orally active methyl-testosterone, this mode of application has been abandoned.

PERCUTANEOUS administration has the disadvantage that the amount absorbed is unpredictable, while INTRAVENOUS and INTRAPERITONEAL administration (not used in man) exert transient effects not suitable for the production of hormonal actions. The anesthetic effects of testoids, on the other hand, are most pronounced after intravenous or intraperitoneal application.

TOPICAL APPLICATION TO ACCESSORY SEX ORGANS, such as the penis, clitoris, seminal vesicles or the capon's comb, cause local growth, thus indicating that the testoids act directly upon the accessory sex organs. However, these methods of treatment seldom have any clinical application.

WITHDRAWAL EFFECTS AND PERMANENT CHANGES CAUSED BY TEMPORARY TREATMENT

Cessation of testoid treatment does not elicit any characteristic WITHDRAWAL EFFECTS comparable to those (withdrawal bleeding, milk secretion) noted after the interruption of ovarian hormone administration. However, the symptoms of the male climacteric (see p. 649) are probably due to a closely related mechanism.

It is noteworthy that PERMANENT CHANGES MAY BE CAUSED BY TEMPORARY TREATMENT with testoids. Thus in women, temporary testoid therapy may cause persistent "masculinization" of the larynx and hence deepening of the voice. The hirsutism caused by testoids is much less likely to persist after cessation of treatment; yet males castrated after puberty continue to grow a beard, while prepubertal orchidectomy prevents beard growth. Apparently the period of hormonal stimulation necessary to cause a permanent change is not the same for each target organ. In very immature or embryonic female animals, excessive treatment with testoids may cause permanent damage to the ovaries and "masculinization" of the accessory sex organs. Indeed, in the rat, even early postnatal administration of testoids can produce pseudohermaphroditic malformations of the genital organs, such as permanent involution of the vagina, uterus and ovaries, with persistent enlargement of the clitoris. Here we are apparently dealing with what might well be called a postnatal malformation.

OTHER PHARMACOLOGIC PROBLEMS AND THEORIES CONCERNING THE TESTIS HORMONES

Other pharmacologic problems concerning the testoids, as well as their biogenesis and fate in the body, will not be reviewed here, since they have been discussed in the section · "The Steroids"

than the Leydig cells and hence, irradiation is recommended for sterilization when maintenance of the endocrine function of the testis is desirable.

EFFECTS OF ORCHIDECTOMY AND TREATMENT WITH TESTIS HORMONES

State. — Orchidectomy causes no very prominent changes in the general condition of the adult patient Climacteric disturbances, comparable to those following ovariectomy in women, are less frequent in men. As with ovariectomy, the younger the individual at the time of orchidectomy, the more striking are the resulting somatic and psychic changes In prepubertally orchidectomized boys, the development of the sex organs (penis, prostate, pubic hair, etc) is markedly inhibited, but after puberty the involution of these organs is much less striking Usually, castrate males are apathetic and tend towards excessive adiposity

Testoids rarely produce any signs of systemic damage. Even excessive amounts are comparatively well tolerated, if treatment is not too prolonged. Complications rarely occur except following chronic treatment with high doses of testoids, especially in elderly men, who may be driven to sexual excesses, to which their bodies are ill-adapted Adrenal deficiency, hypopituitarism and excessive destruction of the liver tend to sensitize the organism to the toxic effects of testoids

In premature infants, testoids are claimed to exert a beneficial effect, perhaps because of the resulting nitrogen retention, which helps the deposition of body protein

Resistance to certain infections and intoxications can also be altered by testoids, it is increased or decreased depending upon the nature of the damaging agent, the dose of the testoid, etc

Temperature. — Neither orchidectomy nor testoid hormone overdosage cause any significant changes in body temperature.

Basal Metabolism. — Orchidectomy tends to decrease the B M.R., while testoids tend to raise it, but these effects are not very marked.

Carbohydrate Metabolism. — Neither orchidectomy nor overdosage with testoids exert any pronounced direct effect upon carbohydrate metabolism.

Lipid Metabolism. — As mentioned above, orchidectomy tends to cause fat deposition. In man, this is particularly conspicuous around the hips and thighs, while in most animals, it is more generalized and often accompanied by fat infiltration between the muscles. It is for this reason that castration has been used, since time immemorial, for the fattening of animals Testoids counteract this tendency towards adiposity. It is very probable that the adiposity is largely, if not entirely, secondary to the general apathy, with loss of libido and fighting instinct, so characteristic of untreated castrates

Nitrogen Metabolism. — Under the influence of testoid treatment the nitrogen balance of animals and man tends to become positive. After discontinuation of this treatment, however, there is an excessive compensatory elimination of urinary nitrogen The nitrogen-retaining activity of testoids appears to be due to their anabolic effect upon body proteins (especially muscle and kidney), and has found clinical applications in the management of cachexia and convalescence, when protein deposition is desirable

Neither orchidectomy nor testoid hormone overdosage cause any significant change in the blood N P.N. Orchidectomy increases while testosterone tends to diminish creatinuria. It will be recalled that loss of creatine through the urine is usually a sign of muscle catabolism. Curiously, methyl-testosterone augments creatinuria and creatinemia in normal as well as in castrate men (though not in all animals).

show signs of normal spermatogenesis, unless they are introduced into the scrotum or under the skin. This is hardly unexpected if we remember that even mere transposition of the mammalian testis, from the low-temperature environment of the scrotum into the warmer peritoneal cavity, causes involution of the seminiferous epithelium (see: "Cryptorchidism", pp. 634, 648, 650).

The chances of success are greater IF WHOLE HUMAN TESTES ARE TRANSPLANTED under the skin (e.g., thigh) by direct vascular anastomosis with the host's arteries and veins respectively. Apparently, permanent takes were frequently obtained with this method during the Second World War, but these cases have not yet been followed long enough, to make certain that the grafts continue to function indefinitely. In any case, in its present form, the technic is not adapted to the restoration of fertility and the great progress in the manufacture of testoids has given us so much simpler and more reliable means of substitution for the endocrine activity of the testes, that transplantation is rarely indicated, except for its possible psychotherapeutic effect.

The testis "takes" more readily in GONADECTOMIZED, than in intact males or females. This is probably due to the fact that in the former there is an excess of the hypophyseal gonadotrophins which are essential for gonadal growth. For the same reason, testicular grafts are rarely, if ever, successful in HYPOPHYSECTOMIZED animals.

TECHNIC OF ORCHIDECTOMY

The technic of orchidectomy (castration in males) is extremely simple, and in most animal species, similar to that recommended for ovariectomy (see: p. 355). Hence, we need not enter into much detail here.

In many animals (especially the mouse and rat, which are most commonly used for bioassays), the inguinal canal remains open throughout life and the testes can be pulled up into the peritoneal cavity. In these species, it is best to make a suprapubic incision in the midline (under ether anesthesia) and to remove the testes together with the epididymis, after placing a ligature around the spermatic cords The vessels of both spermatic cords may even be tied by a single ligature, but some prefer separate ligatures on each side, in order to avoid the possible formation of extensive adhesions, which may obstruct the urinary passages. The removal of the epididymis is recommended, not only in order to avoid the possibility of lesioning the capsule of the testis and leaving some gonadal tissue behind, but also because extratesticular Leydig cell accumulations are occasionally found in the epididymis and these may continue to produce testoids after castration. With some experience, orchidectomy in rodents can thus be performed through incisions no larger than the smallest diameter of the testis and epididymis. Two stitches through skin and muscle layers suffice to close the wound. The operation need not take more than two minutes. The advantage of the suprapubic incision is not only that it gives access to both testes through a single wound, but also that it is less likely to become infected than cuts in the wrinkled irregular skin of the scrotum. Nevertheless, orchidectomy through the scrotum can be performed if the skin is carefully cleaned. In man and in animals whose inguinal canal is closed, only this approach is practical. Absolute asepsis is not necessary in performing castration in birds and rodents since they are very resistant to infection

X-RAY CASTRATION, so frequently performed in women, is rarely indicated in men. It is noteworthy, however, that the seminiferous tubules are very much more sensitive to X-ray damage

erections with ejaculations may persist years after complete castration. In prepubertal castrates, on the other hand, more or less complete absence of libido and sexual impotence are the rule. Treatment with *testoids* tends to increase libido and to restore potency in castrate males, but this therapy is not always effective, since many other factors are important in conditioning sexual behavior. *In females*, treatment with testoids often produces homosexual tendencies, but sometimes it merely stimulates the normal sex drive. This effect is perhaps partly due to the clitoris enlargement and hyperemia, which exposes local sensory nerve endings to constant stimulation As stated in the section "The Ovary," both male and female sex hormones are involved in the regulation of libido in either sex

Adult hens and baby chicks of either sex develop the characteristic FIGHTING INSTINCT of the rooster and their social position in the "peck-order" of a flock rises following testoid treatment. In cocks and even in mammals the fighting instinct tends to diminish after orchidectomy and to increase following testoid administration.

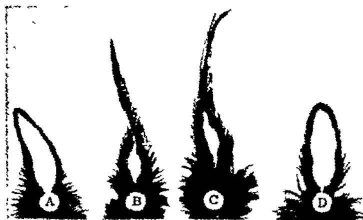
The ANESTHETIC EFFECT of sudden overdosage with excessive doses of testoids is considerably less pronounced than that obtained with equivalent quantities of luteoids or corticoids

Digestive System. — In certain animal species (notably the mouse), testoids cause hypertrophy of the tubular portions of the salivary glands. In liver cirrhosis testoids are often beneficial. Testoids exert no other prominent effects upon the gastrointestinal tract.

Skin and Appendages. — Testoids tend to cause hypertrophy of the SEBACEOUS glands of the skin. Even in women this is often accompanied by acne, apical baldness, beard and mustache growth, and excessive somatic HAIR DEVELOPMENT, with the male type of hair distribution.

The PLUMAGE of gonadectomized (male or female) fowl is not very characteristically affected by testoids, since it is already of the "male" type. It will be remembered that the typical plumage of hens is merely due to an inhibition of the development of "neutral" (cock-like) feathers by ovarian hormones Very large doses of testoids may even cause hen-feathered appearance, presumably as a result of the slight folliculoid potency of the testoid hormones

In certain birds (e g , English sparrow), the BILL COLORING is characteristically black during the breeding season in males, but becomes white during the off-season or after castration. Testoids elicit the dark coloring at any time in intact or gonadectomized birds of either sex.



Effect of sex hormones on plumage in "hen-feathered" breed. — A. Normal saddle hackles of seabright bantam male — B Capon — C. Capon treated with androsterone (same as B) — D. Capon treated with estrone Note that in this hen-feathered' breed, the male normally exhibits the plumage which in castrates is artificially induced by folliculoids not by testoids Castration causes appearance of male feathering normally not seen in either sex

Water and Salt Metabolism. — Neither orchidectomy nor testoid hormone overdosage causes any prominent changes in water and salt metabolism, although high doses of testoids may produce hypopotassemia and edema in man (not in all animals).

Growth and Bone Structure. — Prepubertal orchidectomy tends to increase somatic growth (in man, especially that of the extremities) and to *delay ossification of the junction cartilages.* Since males are normally taller on the average, this effect of gonadectomy is not as striking in them as it is in females.

Moderate doses of testoids also tend to increase somatic growth, while severe overdosage causes growth retardation, due to premature ossification of the junction cartilages. In man, early hypertestoidism results in disproportionately short extremities The comparatively gracile skeletal structure of castrates and the robust bone development in hypertestoidism may be, at least partly, secondary to the deficient muscular development of the former and the increased muscular strength of the latter

Blood. — Neither the blood count nor blood coagulation are significantly altered by orchidectomy or testoid hormone overdosage However, castration tends to delay, and hypertestoidism to accelerate, erythrocyte regeneration after hemorrhage in the rat.

Cardiovascular System. — The cardiovascular system tends to be hypoplastic after orchidectomy, while testoids stimulate its development. It is not known to what extent these effects are secondary to the diminution in muscular activity after gonadectomy, and the increased vigor occasioned by testoid treatment, respectively

In angina pectoris, diabetic gangrene, endarteritis obliterans and climacteric vascular disturbances in women as well as in men, testoids are sometimes used with apparently the same success as folliculoids. But the value of this treatment is still controversial.

The vessels of the male accessory sex organs are specifically stimulated by testoids (e.g., comb and wattles in birds, seminal vesicles, prostate, penis in mammals), but this is merely part of the general action of these hormones upon sexual development.

Lymphatic System. — Orchidectomy tends to enhance the development of the thymico-lymphatic apparatus, while testoids exert an opposite effect. They are, however, much less active in this respect than the folliculoids.

Respiratory System. — Prepubertal orchidectomy prevents the change of voice and the corresponding anatomic transformations which normally occur in the larynx of boys at puberty. This results in the persistence of a high-pitched (soprano) voice throughout life. Testoid hormone administration on the other hand, elicits these changes in the larynx of prepubertal males or females, as well as in adult women. It is noteworthy that the deepening of the voice, being due to organic changes *in the vocal apparatus, does not regress* following cessation of testoid therapy in women, or after castration in adult men.

Muscles. — The better development of the male, as compared to the female musculature can be regarded as an accessory sex characteristic. It is in accordance with expectations, therefore, that orchidectomy inhibits, while testoids augment, the development of the muscular system. This is particularly true of certain muscle groups, which are especially well-developed in males, for instance, the masticatory and peroneal muscles in guinea pigs.

Nervous System. — Orchidectomy tends to cause disappearance of the libido in adult men, but this is not always the case. Sexual desire and even





revealed that this kid
similar castrate mouse
Note great diminution
tion revealed that th

(Courtesy of Dr C. D. Kochakian.)

normally present in one sex only, is merely due to a specific inhibition of their development by the hormones of the opposite sex. The spurs and the brilliant feathers of the rooster have been mentioned as examples of such "neutral" characteristics, which persist after orchidectomy and cannot be evoked by testoids. Their absence in hens is due to the suppressing effect of folliculoids.

In certain breeds of fowl, usually referred to as "hen-feathered" varieties, the plumage is the same in the normal male and female, it is reminiscent of the plumage of the hens in other breeds. In such strains of which the seabright bantam is the most common example, ablation of the testes results in cock-feathering, which does not occur normally in these breeds. Strictly speaking, one should say that the feathers assume the capon type, but the male and the capon type are almost indistinguishable. It appears that the testes of the seabright (and of similar breeds) normally produce folliculoids which cause hen-feathering (see p. 619), or that their feathers are hypersensitive to the folliculoid side-effects of testoids.

The HEAD FURNISHINGS of the rooster (comb, wattles and ear lobes) undergo marked involution after orchidectomy due to shrinkage of their mucoid con-

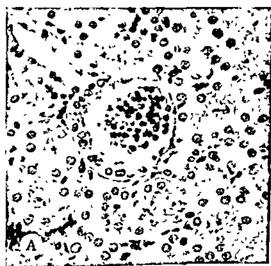
In male anuran amphibia, the characteristic cutaneous THUMB PADS, which play a rôle during the copulatory "clasp reflex," are under testis control. Their glands involute during the off-season, or following orchidectomy, and undergo hypertrophy after treatment with testoids.

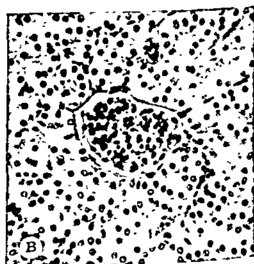
Urinary System. — In many animal species, the KIDNEY of the male is larger than that of the female. In the mouse, the sex difference is particularly characteristic because in males the parietal lamina of Bowman's capsule tends to bear a cuboidal or cylindric, instead of the usual squamous, flat, epithelium. Orchidectomy causes a decrease in renal size, while testoid administration not only restores the volume of the kidney to normal, but can even cause considerable enlargement above normal This is due mainly to hypertrophy of the proximal and distal convoluted tubules, while the glomeruli remain uninfluenced. In the mouse, the characteristic "male type" of parietal capsular epithelium develops in females or castrate males, as a result of testoid administration.

This renotrophic effect is not a subordinate action of the testoid potency; although it is demonstrable in all testoids so far examined, there appears to be no close parallelism between the renotrophic and testoid effects. Unlike the nephrosclerotic effect of certain steroids (e.g., desoxycorticosterone) and anterior-pituitary extracts, the renotrophic action of the testoids is comparatively independent of the dietary sodium and protein intake.

Urinary CALCULI and hyperplastic changes in the epithelium of the BLADDER and URETHRA have also been noted in animals chronically treated with large doses of testoids.

Accessory Sex Organs. — The general characteristics of accessory sex organs have been discussed in the section: The Ovary. (See also: "Skin and Appendages" p. 619.) Let us merely reiterate here that not all accessory sex characteristics are dependent upon positive stimulation by sex hormones. Some, the so-called "neutral" sex characteristics, develop in the absence of sex hormones; the fact that they are

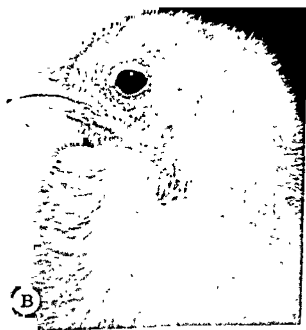




Renotrophic effect of testoids. — A. Kidney of castrate male mouse 25 days after implantation of a 12 mg pellet of methyl-testosterone Note great enlargement of tubular cells and especially of the parietal lining of Bowman's capsule (renal weight 711 mg) — B. Kidney of similar castrate male mouse Note small tubular cells and flat squamous lining of Bowman's capsule (renal weight 322 mg)

— C. and D. Similar 18-day-old chick, following 16 days of treatment with 5 mg of testosterone/day subcutaneously





Effect of testosterone on head furnishing of newly-hatched chick. — A. and B. Normal, 18-day-old chick.
(Cont'd on p 623)

nective tissue stroma. Their normal size is so readily restored by testoids that the enlargement of the capon's comb has been used as a sensitive index of testoid activity in bioassay work.

In mammals, the growth of all male accessory sex organs is, at least partly, under the influence of testoids.

The EPIDIDYMIS undergoes pronounced atrophy after castration. The spermatozoa within its tubules gradually lose their motility and disintegrate, although they may survive for several weeks after orchidectomy. This explains why fertile matings are possible weeks after castration, even in man. Administration of testoids maintains both the structural integrity of the epididymis and the viability of the spermatozoa (spermatogenic effect).

The VAS DEFERENS shows atrophy of its epithelium and fibromuscular wall, following orchidectomy. Testoids not only maintain these structures, but can even stimulate them above normal.

The SEMINAL VESICLES likewise undergo atrophy, both of their epithelial and fibromuscular elements after orchidectomy. Here again, testoids bring about complete restitution to normal. Heavy overdosage with testoids may cause gigantic enlargement of the seminal vesicles, with a considerable increase in their secretory activity This is particularly obvious in rodents, whose seminal vesicles are comparatively large even under normal conditions Because of this great sensitivity, the seminal vesicles of castrate rodents lend themselves especially well for the bioassay of testoids (see p 632).

The PROSTATE epithelium, as well as the voluminous fibromuscular tissue of this gland, involute immediately after castration. Testoids, on the other hand, cause rapid growth not only of the male prostate, but even of the rudimentary prostate possessed by the females of some species (e g, certain strains of rats)

The BULBO-URETHRAL GLANDS (Cowper's glands) respond to orchidectomy and testoid treatment in the same manner as the other male accessory sex organs

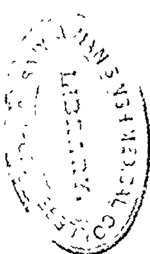
The PREPUTIAL AND MAMMARY GLANDS are normally present in both sexes, although the former are rudimentary in the female, the latter in the male. Both these organs involute after orchidectomy and are stimulated by testoids. This stimulation is potentiated by simultaneous treatment with anterior-pituitary extracts. In this respect, the preputial and mammary glands (which originate from closely related embryologic primordia) differ from the previously mentioned accessory sex characteristics, upon which anterior lobe extracts exert no direct influence

In lactating animals testoids decrease milk production, especially in the presence of the ovary, in spayed females this effect is much less evident.

The development of the PENIS is likewise under testicular control It undergoes atrophy after castration and can be stimulated (even above normal) by testoids. In the guinea pig, there are epithelial excrescences, the so-called "penis thorns," at the tip of the organ These tend to persist for a long time after castration, but if they are clipped off, their normally rapid regeneration fails to occur in the castrate unless testoids are administered. This reaction has also been used as an indicator in bioassay work.

Among other accessory sex organs whose development depends upon the presence of the testis or the administration of testoid hormones, we might mention the ANTLERS of the deer, the HORNS of the goat, the PERIANAL ODORIFEROUS OR SCENT GLANDS (modified sebaceous glands) of the guinea pig, goat shrew, musk-deer, etc All these morphologically so diverse structures respond to the same hormonal stimuli

It is noteworthy furthermore, that even female accessory sex organs are sensitive to testoids





A

Effect of castration on head furnishings of the cock. — A. Head furnishings of a normal adult cock



B

— B. Head furnishings of a similar cock two months after castration. Note atrophy of comb, ear lobes and wattles

property, as well as the general feeling of vigor associated with sexual stimulation, may also be responsible for the so-called *rejuvenating* effect of these hormones.

Tumorigenesis. — Since orchidectomy often causes at least temporary improvement in patients with carcinoma of the prostate, it has been claimed that excessive endogenous production of testoids may be responsible for this type of cancer. It has not been possible, however, to produce true neoplasms with testoids in experimental animals or man.

The tumorigenic effects of folliculoids, especially the production of anterior-lobe adenomas and uterine fibromas are inhibited by simultaneous treatment with testoids

METABOLISM OF THE TESTIS HORMONES (TESTIS HORMONE CONTENT OF BODY FLUID AND TISSUES)

The main problems in connection with the metabolism and biogenesis of the testis hormone have already been discussed in the section : The Steroids. Variations in the testis hormone content of the blood and urine have also been mentioned in connection with those diseases in which they are of diagnostic importance (see especially chart on p. 129). Here we shall merely summarize the main pertinent facts.

Biogenesis and Fate of the Testis Hormone. — Under normal circumstances only the testis and the adrenal cortex produce important amounts of testoids, although probably the ovary (and perhaps even the placenta) can also elaborate some

Testoid production by the TESTIS requires no further discussion

That the ADRENAL CORTEX can produce testoids is suggested by many experiments In castrate rats the prostate and seminal vesicles were caused to develop under the influence of corticotrophin; since this hormone exerted no such effect after adrenalectomy it was deduced that the adrenal cortex produces testoids under the influence of the corticotrophic principle.

If gonadectomized during the first days of life, male or female mice (of susceptible strains) tend to develop adrenal tumors These produce testoids as shown by the growth of the accessory-sex-organs

Castration of newborn male rats does not arrest the growth of the seminal vesicles and prostate until about the 5th week of life unless the adrenals are also removed.

Gonadectomized men and women continue to excrete considerable quantities of testoid and 17-KS materials (especially androsterone and dehydroiso-androsterone) in the urine, and adrenal-cortical proliferation (hyperplasia or tumors) is frequently conducive to virilization. All these observations confirm that the adrenal cortex can produce testoids and indeed it has been demonstrated that a variety of testoid and other 17-KS substances can be isolated from the adrenal cortex in chemically pure form (see : chart on p. 80 and 81).

Testoid production by the OVARY is likewise highly probable. Certain lipid-soluble ovarian extracts contain testoids as judged by standard bioassays Furthermore, experiments on castrate male mice and rats with ovarian transplants in their ears, revealed that such grafts maintain the male accessory-sex-organs, presumably because they produce testoids The low temperature under the skin of the ear seems to be important for the ability of ovarian tissue to produce testoids since similar grafts placed into the abdomen were not equally active.

Thus the UTERUS AND OVIDUCT are stimulated by testoids in most animal species. Their musculature and mucosa undergo changes similar to those obtainable by simultaneous treatment with folliculoids and luteoids. Some testoids (e.g., methyl-testosterone and especially ethynyl-testosterone) possess a high degree of luteoid potency, while others (e.g., testosterone) which are less active in this respect, produce responses more like those caused by folliculoids.

It is noteworthy that the *human endometrium* becomes atrophic as a result of testoid administration, a reaction similar to that seen in pseudohermaphroditism due to virilizing adrenal (cortical adenomas or carcinomas), or ovarian (Leydig cell, other "lipid-cell blastomas," etc.) tumors.

The VAGINA of most animals undergoes proliferative changes under the influence of testoids. In the common laboratory rodents (e.g., rat, mouse) there is a transitory phase of cornification, but under continued treatment the epithelium becomes mucified and very similar to that of animals treated with luteoids

The *human vagina* on the other hand, undergoes atrophy and loses its glycogen granules, as a result of testoid administration.

The CLITORIS is greatly stimulated by testoids in animals as well as in women, demonstrating that this organ is not only embryologically related to the penis, but even responds to the same hormonal stimuli

The above-mentioned changes in the accessory sex organs are greatly dependent upon the AGE of the recipients In female embryos, treatment with testoids (administered to the mother) causes severe pseudohermaphroditic malformations of the genital organs. The clitoris and preputial glands are enlarged, while the uterus and vagina remain atrophic. Even during very early postnatal life, treatment with testoids may cause similar permanent deformities (e.g., rat).

There are only very few instances of a true peripheral ANTAGONISM BETWEEN MALE AND FEMALE SEX HORMONES. The atrophy of the male accessory sex organs produced by folliculoids is almost invariably due to "*functional castration*" by inactivation of the Leydig cells. However, the atrophy of the comb caused by folliculoids in cocks is, at least partly, due to a true antagonism at the target organ Comb growth is impeded at the site of inunction with folliculoid substances even in testosterone-treated capons. (For other instances of such antagonisms see : The Steroids.)

Sexual Cycle. — Treatment with testoids interrupts the sexual cycle, partly because of the resulting ovarian changes (see: Stimuli Influencing Ovary. p. 379), and partly because of the direct action of testoids upon the uterus and vagina.

Pregnancy. — Testoids tend to cause abortion in certain animals (e.g., rabbit), while others tolerate them comparatively well during gestation (e.g., man, rat): in the offspring of the latter they produce pseudohermaphroditic changes as stated above

Lactation. — Large doses of testoids interrupt milk secretion, although they stimulate the development of the mammary glands (See "Accessory Sex Organs," p. 625.)

Hibernation. — Orchidectomy and testoid hormone overdosage exert no significant effect upon the winter-sleep of hibernating animals. The normal involution of the gonads during this season is merely secondary to the changes in hormone secretion characteristic of hibernation.

Regeneration and Rejuvenation. — Several investigators claimed that wound healing and other regenerative processes are accelerated by testoids, perhaps due to their nitrogen-retaining protein-anabolic action. This latter

property, as well as the general feeling of vigor associated with sexual stimulation, may also be responsible for the so-called rejuvenating effect of these hormones.

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That ovarian tumors can produce virilizing material has been mentioned elsewhere.

Little is known about the PRECURSORS from which the organism makes testosterone. When a variety of comparatively weak testoids (presumably precursors of testosterone) were added to blood perfused through bull's testes, the testoid potency of the perfusate increased, no such augmentation of activity could be obtained with testosterone itself. It is possible that here the testis tissue transformed other, less active, steroids into testosterone but this has not been definitely proven. (For data concerning the anabolism of steroids in general, see: pp. 76-78.)

More is known regarding the CATABOLISM of the testis hormone, testosterone. Following enteral or parenteral administration of testosterone, much of it is completely catabolized, but increased urinary elimination of androsterone, iso-androsterone, etiocholane-3(α)-ol-17-one and other 17-KS has also been demonstrated (in a variety of species). Methyl-testosterone, on the other hand, actually diminishes 17-KS elimination; presumably because the methyl side-chain is not split off during metabolism Thus the compound itself is not transformed into 17-KS, yet, through the mechanism of "compensatory atrophy," it diminishes the production of endogenous testoids.

A large portion of the urinary testoid material is eliminated in a partially inactivated form as sulfate esters (e g, dehydro-iso-androsterone sulfate, androsterone sulfate). Acid hydrolysis splits these esters into the active free steroids.

Like most steroids, testosterone and other testoids are inactivated in the liver although other tissues may also participate in this process. It is presumably, at least partly, for this reason that testosterone is much more active when given parenterally than when administered per os or by intrasplenic implants In the latter case the compound has to be absorbed through the portal circulation and hence is immediately subjected to hepatic detoxification. Compounds such as methyl-testosterone, which are comparatively highly active per os, have been claimed to be more resistant against hepatic detoxification. However, the great oral efficacy of methyl-testosterone may also be due to its slower (and hence more economic) absorption rate, which assures prolonged activity before the active material is eliminated through the urine or destroyed in the body.

During the chemical procedure of extraction, urinary steroids may be transformed into compounds not normally occurring in the body. (In the table, on pages 82 and 83, those urinary steroids which are presumably artefacts, have been so labelled.)

Occurrence of Testoids and Other 17-KS in Body Fluids and Tissues. — The steroids which have been isolated, in chemically pure form, from TESTIS tissue are listed in Table III (p. 84). It is especially noteworthy that Δ^5-pregnenolone is present in the testis, since this compound is not testoid but highly spermatogenic. Perhaps it is also a testis hormone

In the BLOOD the presence of testoids has been demonstrated by the usual capon-comb test. However, no systematic studies concerning the testoid and other 17-KS of the blood are on record.

Especially extensive investigations have been performed on the testoid and 17-KS content of the URINE under normal and abnormal conditions both in man and in animals (See pp. 82 and 83)

Normal adult men excrete about 70 I U/day of active testoid material, but the daily amount varies considerably; a range of 20-120 I.U./day is considered normal. The total neutral (that is non-phenolic) 17-KS elimination of

normal adult men is about 10-15 mg./day (Callow's method) or 16-34 mg. (Holtorff and Koch method) depending upon the technic used.

In normal adult women the daily testoid elimination averages about 20-50 I.U./day, that is, about 30% less *than in men.* The 17-KS excretion of normal adult women is about 7-12 mg./day, with a mean of 9.5 mg./day (Callow's method), or 5-22 mg. with a mean of 13 mg./day (Holtorff and Koch method). *It is noteworthy that* the menstrual cycle does not significantly influence testoid and 17-KS elimination

The testoid and 17-KS elimination *of animals* (*e g., stallion, bull, ram, rat,* rhesus monkey, chimpazee) varies between 1-5 I.U./L and hence is considerably below that of man

The urine of *castrate or eunuchoid men* contains about 10 I.U./day of testoid activity and approximately 3-13 mg./day of 17-KS, that is, considerably less than normal.

The urine of *eunuchoid women* possesses about 1/3 the normal 17-KS concentration. Soon after *ovariectomy* the urinary 17-KS and testoid content *is* unchanged, but occasionally, years after the operation, these values actually rise several hundred per cent above normal This is somewhat reminiscent of the virilizing adrenal growths induced *in* mice by gonadectomy (see above).

These findings indicate that the 17-KS excretion of gonadectomized men and women becomes approximately the same *It has been concluded that* the adrenal cortex produces essentially similar amounts of testoids in both sexes.

Curiously, in monkeys even simultaneous *gonadectomy and adrenalectomy* fail to abolish urinary 17-KS elimination completely, hence it appears that *perhaps* some tissue, outside the gonad and adrenal cortex, can also produce such steroids

In *Addison's disease* the testoid and 17-KS excretion falls to very low levels in both sexes. In some female addisonians no 17-KS are detectable in the urine.

Among the *hypophyseal diseases,* 17-KS and testoid elimination in the *urine falls to extraordinary low levels* in Simmonds' disease, while in acromegaly and Cushing's syndrome unusually high levels are found.

In *adrenal-cortical hyperplasia and tumors* the urinary excretion of testoid and 17-KS may reach extraordinarily high levels The highest concentration of 17-KS ever observed in the urine of man, was found in a 30-year-old *woman with a metastasizing adrenal-*cortical cancer, it was 2100 mg. of 17-KS/day!

Hirsutism in women is also frequently accompanied by increased 17-KS elimination, *but,* since *the* cause of this anomaly is not always the same, it is understandable that the derangement in steroid metabolism is likewise variable

Testis tumors consisting of Leydig cells, considerably raise urinary 17-KS and testoid elimination In one pertinent case as much as 1000 mg. of 17-KS/day could be demonstrated in the urine.

Virilizing ovarian tumors tend *to* increase the elimination of testoids and 17-KS, but certain arrhenoblastomas cause virilization without any rise in 17-KS excretion.

Among other diseases *hypertension, diabetes, myxedema* and *thyrotoxicosis* are often accompanied by a diminution in 17-KS elimination. The same is true of prolonged *starvation* or any other *type of stress.*

Gonadotrophins cause only a moderate rise in testoid and 17-KS elimination in man and practically none in animals.

For urinary elimination of exogenous *testoids* *see p. 628.*

Administration of *corticoids,* especially desoxycorticosterone, was shown

to raise 17-KS excretion in addisonians, as well as in ovariectomized monkeys. Perhaps corticoids can be transformed into 17-KS by oxidative degradation of their side-chain

Folliculoids considerably diminish testoid and total 17-KS excretion, presumably because they cause Leydig cell atrophy.

Under six years of *age* only negligible amounts of testoids and 17-KS are eliminated in the urine of boys, but with the onset of puberty the titer rises to about 28 I.U./day at 17-18 years, the adult level (see above) not being reached until about 20-22 years of age. In girls the output is not significantly different before puberty.

In old men and women the urinary testoid and 17-KS elimination decreases and at the age of 60-70 years generally only 1/3 to 1/10 the normal amount is eliminated.

During *gestation* there appears to be a slight, but continuous, rise in 17-KS and testoid elimination both in women and in the monkey.

Dogs bearing biliary fistulæ excrete comparatively large amounts of testoids in the *bile* following a single injection of androsterone or testosterone.

STIMULI INFLUENCING TESTIS STRUCTURE

Extirpation of Endocrine Glands. — HYPOPHYSECTOMY causes pronounced involution of the testis in all vertebrates. Both the seminiferous epithelium and the Leydig cells are affected by the deficiency in hypophyseal gonadotrophins.

Administration of *hypophysoid gonadotrophins* permits the restoration of the atrophic testis The pertinent literature is somewhat contradictory, partly because some species (e.g., fish, amphibia, reptiles) are comparatively insensitive to hypophysoids of other species and partly because many of the extracts used were very impure The following are the best established facts, which in principle, apply to all species, although they are mainly based on experiments in the rat :

(1) *FSH* prevents the involution of the spermatogenic epithelium if it is given immediately after hypophysectomy; if administered later it can even restore spermatogenesis after tubular atrophy has set in. Pure FSH does not appear to influence testis hormone secretion.

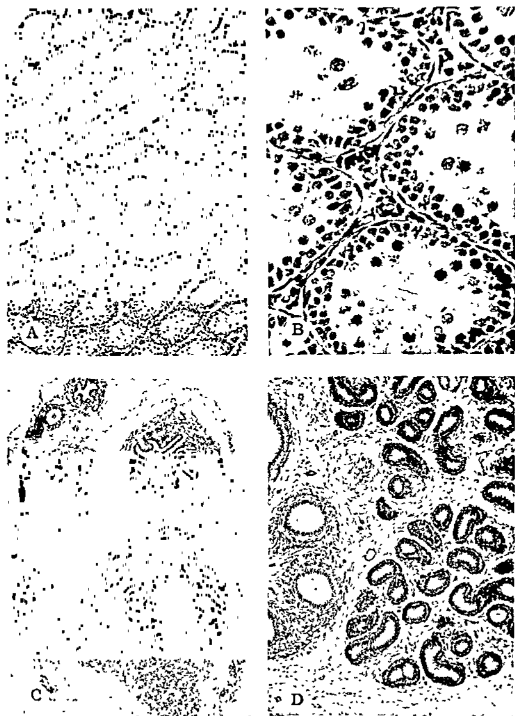
(2) *LH* does not stimulate the spermatogenic epithelium. It causes hypertrophy and hyperplasia of the Leydig cells, accompanied by an increased testoid production, as judged by the enlargement of the accessory sex organs, which are under the control of testoids.

(3) *FSH plus LH*, given in suitable proportions, restore both spermatogenesis and Leydig cell development after hypophysectomy

(4) *Luteotrophic hormone (prolactin)* exerts no detectable influence upon the structure of the testis in hypophysectomized animals.

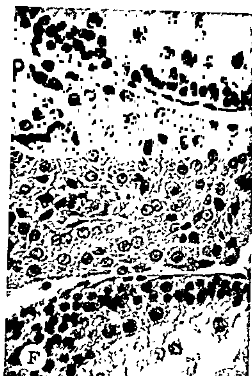
(5) *Spermatogenic steroids* maintain the spermatic epithelium, if administered immediately after hypophysectomy, and can even restore it, if given some time after involution has occurred. This restoration of the spermatogenic cells is not necessarily accompanied by any change in the atrophic accessory sex organs. It had initially been thought that only testoids were capable of exerting a spermatogenic action, but Δ^5-pregnenolone, progesterone and other non-testoid steroids likewise exhibit this effect, so that the spermatogenic action appears to be independent of the testoid potency (See. "The Steroids.")

In some animals (e g., rat) in which the peritoneal cavity continues to communicate with the scrotum during postnatal life, hypophysectomy causes



Effect of hypophysectomy and replacement therapy upon the testis and accessory sex organs — **A.** Atrophy of seminiferous tubules and Leydig cells 28 days after hypophysectomy in an adult male rat (low magnification) — **B.** Region from Fig A under higher magnification Note atrophic Leydig cells and absence of mature stages of spermatogenesis in tubules Only the Sertoli cells, spermatogonia and primary spermatocytes are preserved in the absence of anterior-lobe gonadotrophin — **C.** Atrophic seminal vesicle of rat shown in Figure A — **D.** Atrophic epididymis of rat shown in Fig A (Cont d on pp 632-633)









— **E.** Testis of hypophysectomized rat similar to that shown in Fig A, but treated with 100 I U of LH (pregnancy urine preparation) subcutaneously, daily during 14 days Note great proliferation of Leydig cells, but no change in seminiferous tubules — **F.** Region from Fig E under higher magnification Note hypertrophy and hyperplasia of Leydig cells, without restoration of tubular epithelium — **G.** Seminal vesicles of rat shown in Fig E Note that under the influence of the Leydig cell stimulation, the secretory epithelium is restored to normal — **H.** Epididymis of rat shown in Fig E Note that under the influence of the stimulated Leydig cells, the epididymis is restored towards normal (Cont'd on p 633)





— I. Testis of a hypophysectomi 50 I U of a pregnant mare serum the influence of the combined treat are stimulated — J Testis of a h treated with 12 mg of Δ^5-pregnenolone (absorbed ... of 50 mg). Note that this spermatogenic steroid selectively stimulates the seminiferous epithelium, without influencing the Leydig cells The accessory sex organs of this animal remained atrophic

cryptorchidism; the scrotum involutes in the absence of functional Leydig cell tissue and the atrophic testis is pushed back into the peritoneal cavity. Treatment with pure FSH does not influence this phenomenon (as it causes no testoid secretion), but spermatogenic testoids or LH, cause descent of the testis into the scrotum. The scrotal sac enlarges again under the influence of the testoids, whether these are injected or liberated by the Leydig cells. Apparently both the mechanical distension by an approximately normal-sized testis and the humoral stimulus of testoid hormones are necessary for the physiologic development of the scrotal sac.

Some involution of the seminiferous and Leydig cells occurs even in prepubertal animals following hypophysectomy This indicates that the male gonad is under the trophic influence of the anterior-lobe, even before sperm formation commences.

Apart from the hypophysoid and spermatogenic principles, no hormone preparation is known to restore any of the testicular elements following their atrophy after hypophysectomy.

Parabiosis of a hypophysectomized male rat with a gonadectomized (male or female) partner, suffices to maintain both the Leydig cells and the spermatogenic epithelium in the hypophysectomized twin This is due to the excess of gonadotrophins coming from the castrate twin Injection of folliculoids, testoids or luteoids into the gonadectomized partner interferes with the testis maintenance in the other twin, owing to the depressing influence which such compounds exert upon the gonadotrophin production of the anterior-lobe

PARTIAL TESTIS EXTIRPATION, especially in young animals, is followed by compensatory hypertrophy of the remaining testis tissue. Usually the regeneration of the spermatogenic elements is more pronounced than that of the Leydig cells. In the fowl there may even be seminoma-like proliferation of the spermatogenic epithelium after partial castration. In general, however, the compensatory regeneration of the testis is not as pronounced as that of the ovary following comparable degrees of partial gonadectomy.

The motility of the spermatozoa, collected from the epididymis, is maintained for several weeks after complete castration in the rat. Later, the spermcells degenerate in the absence of testicular hormones. After unilateral castration, the spermatozoa in the ipsilateral epididymis survive longer, apparently due to testis hormone production by the contralateral gonad Even after bilateral castration, the survival of the spermatozoa in the epididymis may be prolonged by the administration of spermatogenic steroids.

Since testoids are also spermatogenic, the maintenance of sperm-motility in the epididymis of castrates has even been used as the basis of a bioassay for testoids.

Artificial CRYPTORCHIDISM, produced by transposing the testis into the abdominal cavity (without lesioning the ductus deferens or the vessels) leads to degeneration of the spermatogenic epithelium with the formation of polynuclear giant-cells from immature spermatocytes Sperm formation ceases, but the Leydig cells remain normal for many months and may even hypertrophy. Their testoid production is likewise maintained or perhaps even increased, as judged by the good development of the accessory sex organs and the often increased libido

The degeneration of the spermatogenic epithelium is generally ascribed to the comparatively high temperature of the peritoneal cavity, as compared with that in the scrotum. (See "Temperature," p. 641.) It is noteworthy, however, that in many animal species (fish, amphibia, reptiles, birds), the testes are normally situated within the abdominal cavity. Most such physiologically cryptorchid species are poikilothermic and thus have a low body temperature; birds, however, have a high temperature, and hence, evidently their testes are not heat sensitive

Neither hypophysoids nor spermatogenic steroids are capable of maintaining spermatogenesis in the cryptorchid testes of mammals.

It has been claimed that spontaneous testicular tumors occur more frequently in cryptorchid than in normal testes.

Following LIGATURE OF THE VAS DEFERENS, ("VASOLIGATION") the tubular tissue degenerates, perhaps due to the pressure exerted by the large number of spermia which accumulate within the lumina. Many spermia enter the epididymis and produce so-called "sperm cysts" by dilatation of its duct system. At a later stage, however, in most animal species, the tubules regenerate again if the testis is not damaged by incidental direct trauma. It has been claimed that following vasoligation the Leydig cells actually proliferate, and that at least a temporary hypertestoidism may thus be produced. It is possible that after vasoligation or cryptorchidism, absorption of the degenerating spermatogenic epithelium may furnish trophic substances for the Leydig cells. However in both these conditions the tubular tissue involutes and it is difficult to estimate whether an apparent increase in the Leydig cell tissue is real, or merely simulated by the greater prominence of the interstitial cells amidst the shrunken tubules.

In senile men, *Steinach* (1920) claimed to have caused "re-activation" of the interstitial cells by vasoligation and advocated this intervention for "rejuvenation" However, most subse-

quent workers could not confirm his *results* and it was emphasized that even congenital defects of the ductus deferens do not necessarily cause any structural abnormality in the human testis.

EXTIRPATION OF THE ACCESSORY SEX ORGANS (e g., the wattles and comb in birds, the seminal vesicles and prostate *in mammals)* is claimed by some authors to cause testis enlargement, but others could not confirm this.

EXTIRPATION OF OTHER ENDOCRINE GLANDS fails to cause any lesions in the testes, beyond the atrophy accounted for by the general-adaptation-syndrome which is elicited by the surgical operation itself or by the resulting metabolic disturbances. There is some indication that *pinealectomy* may elicit precocious puberty in male animals (see: p 594), but this claim requires confirmation

EYE EXTIRPATION or local irritation of the eye (by alcohol, pepper, etc.) may cause an increase in testis size in birds, especially the duck This is ascribed to the local irritation produced, and is compared with the testis-stimulating effect of artificial illumination. In drakes, testis growth can be obtained during the non-breeding season by illumination with red and infrared rays. This is not prevented even by complete enucleation of the eyeballs, apparently because these rays penetrate the orbit. Even prepubertal drakes can be brought to puberty by such artificial illumination (See "Rays," p 642.) If, after removal of the eye, the orbital cavity is completely blocked by a rubber pad, the effect of light is greatly diminished or abolished; the slight stimulation which persists can be ascribed to penetration by rays of the thin cranial bones. Direct illumination of the pituitary, by light applied to it through a light-conducting rod, also causes testis maturation When thus directly applied, blue rays proved just as effective as red rays, although, under ordinary conditions, the latter are much more active (*Benoit, 1936*). Using this method, it was possible to demonstrate that direct illumination of the hypothalamus or rhinencephalon are also effective, as judged by the resulting testis enlargement.

In mammals, operations on the eye do not noticeably influence testis development.

Experimental HEPATIC LESIONS OR DEVIATION OF THE BILE THROUGH A FISTULA may cause testicular atrophy in the rat, perhaps because bile is essential for the absorption of vitamin-E

Hormones. — HYPOPHYSOID GONADOTROPHINS exert essentially the same effect in the intact as in the hypophysectomized animal (see p. 630). It is noteworthy, however, that while *LH* is very effective in over-stimulating Leydig cell development and function, spermatogenesis is less readily augmented above the physiologic limits by *FSH*. Prepubertal mammals are more sensitive than adults to the characteristic affects of FSH and LH upon the spermatogenic and Leydig cells respectively. This is merely another instance of the rather general rule that hormones are most effective when their level in the body fluids and tissues is low.

Immature birds (e g., chick, duck, pigeon) are singularly insensitive to the direct (testis) and indirect (*accessory-sex-organ* stimulating) effect of LH.

Following very chronic treatment with hypophysoid gonadotrophins the testis involutes presumably due to antihormone formation.

It has been claimed that at least in birds (e.g., pigeon), *luteotrophin* (prolactin) causes testis involution, perhaps through an inhibition of *FSH* production by the animals' own pituitary. In mammals prolactin has no effect upon the testes

Hypophysoids and *folliculoids* mutually antagonize each other's effect upon the testis. The atrophy of the germinal epithelium and Leydig cells,

normally produced by folliculoids is readily counteracted by FSH and LH respectively. Folliculoids act merely by depression of the gonadotrophin production of the animal's own pituitary, without exerting any significant direct effect upon the testis; hence they do not interfere with the testis-stimulation by hypophysoids, if large amounts of the latter are given.

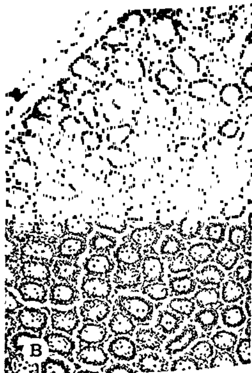
FSH and LH in suitable doses, also counteract the testicular atrophy normally produced by various types of *non-specific damage.* They cannot prevent, however, the testicular atrophy resulting from *E-avitaminosis.*

In the undeveloped testes of dwarf mice, LH and FSH induce spermatogenesis and Leydig cell development, demonstrating that the *hereditary* defect of this race does not affect the hormone sensitivity of the testes, but merely the anterior-lobe hormone production. In animals with *seasonal* breeding periods, hypophysoid gonadotrophins induce testis development during the off-season.

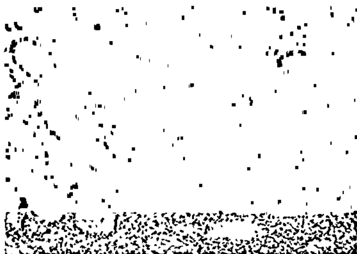
The degeneration of the seminal epithelium caused by *X-rays,* is not influenced by hypophysoid gonadotrophins. The Leydig cells, on the other hand are comparatively X-ray resistant and they can be stimulated by such hormones, even in a testis whose spermatogenic epithelium is completely destroyed.

FOLLICULOIDS cause involution of both the spermatogenic epithelium and the Leydig cells, but various species are not equally sensitive to these effects Thus, mice are singularly resistant to the anti-spermatogenic and anti-Leydig-cell actions of folliculoids; indeed, certain hereditarily predisposed strains respond inversely with hyperplasia of the interstitial cells. This may even proceed to the formation of transplantable, malignant, metastasizing

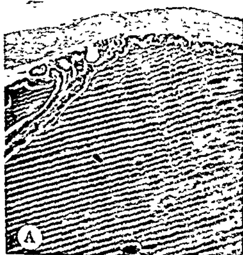


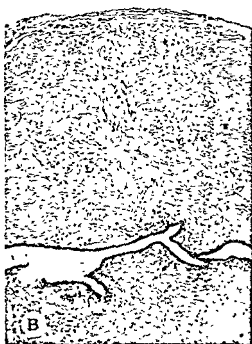


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ıe testis of a susceptible (an artificial folliculoid) cells The few remaining ıer strains do not develop such tumors, when similarly treated (Courtesy of Dr W Gardner)





Effect of folliculoids upon seminal vesicles. — A Seminal vesicle of normal adult rat Note thin muscular wall, lined by well-developed, high cylindric epithelium The lumen is filled with secretion (the latter becomes brittle during fixation and shows parallel lines of fragmentation which are artefacts). — B. Seminal vesicle of an adult rat, treated with 100 γ/day of α-estradiol during 6 months Note great fibrosis and thickening of the wall, atrophy of lining epithelium and absence of secretion in lumen

Leydig cell tumors and hypertestoidism (*Gardner*).

The anti-spermatogenic — but not the anti-Leydig cell activity — of folliculoids is counteracted by spermatogenic steroids (see : p. 64).

In embryos, especially those of lower vertebrates such as fish, amphibia and birds, treatment with folliculoids can cause a partial transformation of the testis into an ovary-like structure. Ovarian tissue develops especially readily in the cortical part of the gonad due to a second proliferation from the germinal epithelium, similar to that seen in genetically female normal animals (*Willier, Dantchakoff, Domm et al.*). The feminization is not necessarily permanent, however, since sometimes chicks feminized by folliculoid treatment of the ovum and hatched with hermaphroditic gonads, may later revert to the normal male type and develop fertile testes In embryonic mammals, folliculoids given to the mother interfere with the development of the testis, but signs of feminization are generally limited to the accessory sex organs. The testis itself remains in the typically female, pelvic position, but, though atrophic, does not contain any characteristic ovarian tissue.

LUTEOIDS exhibit some spermatogenic action: hence, combined treatment with folliculoids and luteoids results in little, if any, testis atrophy. It is because of their spermatogenic action that luteoids given alone likewise fail to cause marked involution of the spermatogenic epithelium, although they possess some folliculoid activity. The latter manifests itself by the Leydig cell atrophy (a "non-inhibitable folliculoid action"), which is not counteracted by their spermatogenic potency

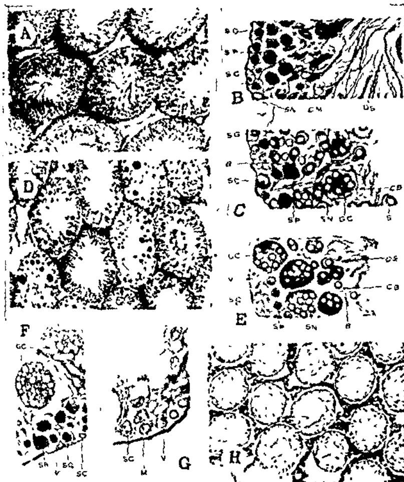
TESTOIDS, given in small doses, cause degeneration of the spermatogenic epithelium and Leydig cell atrophy, while large doses exhibit only the latter effect. This has also been ascribed to the presence of both folliculoid and spermatogenic potency in the testoids (e.g., testosterone, methyl-testosterone), the former prevailing at low, the latter at high dose levels (see . page 65). In man, testoids tend to decrease the sperm count, and may temporarily decrease fertility but they rarely elicit any severe testis atrophy.

Unlike after hypophysectomy or hyperfolliculoidism, the SPERMATOGENIC STEROIDS do not restore testes damaged by cryptorchism or X-rays: they also fail to stimulate spermatogenesis much above normal.

Diseases. — The various forms of HYPOPITUITARISM (e.g., pituitary dwarfism, Simmonds' disease, adiposo-genital syndrome), cause involution, both of the seminiferous epithelium and of the Leydig cells. However, most other serious chronic diseases (e.g., Addison's disease, severe myxedema or hyperthyroidism, diabetes mellitus and infectious diseases, especially tuberculosis) cause essentially similar testis lesions, due to the resulting general-adaptation-syndrome, with the characteristic decrease in gonadotrophin secretion.

LIVER DISEASES, especially cirrhosis, are frequently associated with testis atrophy and gynecomastia. It has been claimed that vitamin-E absorption is impeded by diminished bile production and that the testicular atrophy is due to the resulting avitaminosis. The gynecomastia is generally ascribed to decreased sex hormone (especially folliculoid) inactivation by the damaged liver. The testis involution often associated with HEMOCHROMATOSIS may likewise be due to accompanying liver damage

PINEAL TUMORS can cause precocious puberty with excessive development of both seminiferous and Leydig cells. It is improbable, however, that these changes are caused by a specific pineal hormone, since they occur even if the tumor arises in brain regions adjacent



Testis degeneration in the Vitamin-E deficient rat. Key SG, spermatogonia. SC, Sertoli cells. SP, spermatocytes. SN, spermatid nuclei. GC, giant cells. DS, degenerate sperm tails — A. Early stage of degeneration, showing clumping and fusion of spermatozoa — B. Enlarged view of germinal epithelium showing these changes in greater detail — C. Later stage, showing loss of spermatozoa and early fusion of the bead-like spermatids. — D. More advanced degeneration showing conditions characteristic of those presented in detail in Fig C and E — E. Large giant cells formed by fusion of abnormal spermatids — F. More advanced injury of the germinal epithelium, showing giant cells undergoing dissolution and abnormal changes appearing in the spermatocytes and spermatogonia — G. The germinal epithelium after complete degeneration, showing the syncytial nature of the Sertoli tissue — H. Lower ma-
This rat received vitamin-E therapy for any arrest or repair of the degenerative process
(After Karl E Mason in Allen et al Sex and Internal Secretions ' Williams and Wilkins 1939)

to the pineal or if the neoplasm completely destroys the pineal tissue

CHORIONEPITHELIOMAS of the testis are often accompanied by excessive Leydig cell development in the contralateral gonad *This is probably* due to the LH produced by the chorionepithelioma cells

MUMPS often causes orchitis followed by testicular atrophy The Leydig *cells and the* accessory sex organs may remain normal in such *patients*, even though the seminiferous epithelium involutes

The testicular lesions which are typical of the various clinical forms of HYPO- or HYPERTESTOIDISM are discussed in the sections devoted to the latter

Diet. — The testis is very sensitive to qualitative or quantitative changes in food intake. Prolonged FASTING OR MALNUTRITION cause atrophy both of the seminiferous epithelium and of the Leydig cells in various animal species.

In man, undernourishment *also* produces *marked* testis involution and among undernourished boys, cryptorchidism and orchitis are comparatively common.

OVER-FEEDING may also cause testis atrophy. This is particularly pronounced in fattened geese or ducks, in

which the seminal epithelium shows pronounced involution, although the Leydig cells may remain in good condition.

Various QUALITATIVELY INADEQUATE DIETS (vitamin, amino-acid, protein, salt deficiencies, etc.) likewise interfere with spermatogenesis and the maintenance of the Leydig cells. Here again, the increased production of corticotrophic and, perhaps also, of other pituitary hormones, during the resulting general-adaptation-syndrome, probably occurs at the expense of a diminished gonadotrophin production.

Among the dietary factors, only *vitamin-E deficiency* appears to exert a truly specific effect upon testis structure. It causes involution of the spermatogenic epithelium, but does not affect the Leydig cells. There is formation of syncytial giant-cells, due to fusion of abnormal spermatocytes and spermatids, with degeneration of the primary spermatocytes and spermatogonia. The tips of the Sertoli cells which contain the spermatozoa often break off and appear in the lumina of the tubules or the ejaculate. Eventually, the seminiferous tubules are lined only by a Sertoli-cell syncytium. The sperm first loses its motility and later fused groups of sperm-cells appear in the ejaculate; finally, the ejaculate is free of spermia. These changes naturally lead to complete sterility.

It is very characteristic that prophylactic administration of vitamin-E concentrates or pure α-tocopherol prevents the occurrence of testis degeneration and maintains fertility for long [illegible] eration has occurred, subsequent administration of vitamin-E rarely restores the structure of the seminiferous epithelium to normal, even if treatment is initiated concurrently with the first appearance of the histologic changes. This irreversibility of the change is likewise very characteristic. Male rats deprived of vitamin-E from the beginning of life require α-tocopherol prior to the 40th or 50th day of age, in order to prevent irreversible involution of the germinal epithelium.

Nervous Stimuli. — Denervation of the testis, transection of the hypophyseal stalk or of the olfactory bulbs, and various operations on the cerebral hemispheres, exert no specific effect upon the testicular structure or fertility.

The sterility which sometimes follows extensive sympathectomy is due to interference with the mechanism of ejaculation and not to any morphologic change in the testis itself.

Periarterial sympathectomy or "chemical sympathectomy," (destruction of the periarterial sympathetic nerves by painting them with certain corrosive fluids), far from causing testis involution, has been claimed to increase the endocrine activity of the Leydig cells, and to produce "rejuvenation" (*Doppler* operation). This stimulating effect is inconstant and rather transitory however, and probably results from the local hyperemia due to vasodilatation.

The pronounced testis involution seen following extensive operations on the central nervous system, as well as that observed in men who died after prolonged emotional strain (e.g., in battles, executions) is probably merely a part of the general-adaptation-syndrome elicited by such strong stimuli.

Age. — In certain lower vertebrates (e.g., fish, amphibia) the testis differentiates late in life. In early larval stages, the male gonads often possess female elements which subsequently involute long before the attainment of sexual maturity.

In late human embryos, the Leydig cells are well developed, perhaps because of maternal gonadotrophins. However, during early postnatal life they involute and remain small until just before sexual maturity. In most mammals, including man, testis develop-

ment proceeds very slowly until puberty, at which time both the Leydig cells and the seminiferous epithelium undergo rapid growth and differentiation. The testis tubules have no lumen in boys younger than 12 or 13 years of age.

The weight of the human testis is about 0.2 gm. at the end of the first, 1.0 gm. at the end of the thirteenth and 20-25 gm. at 18 years of age.

In old men, spermatogenesis may proceed until 70-80 years of age, but frequently senile atrophy occurs much earlier.

Constitution, Race, Heredity. — In dwarf strains of mice, only the first stages of spermatogenesis are detectable. These, we know from observations on hypophysectomized animals, are independent of hypophysoid gonadotrophins.

In man, racial and constitutional factors markedly influence testis structure. Thus in the Japanese, the two testes with their epididymides average 12 gm. which is about half the weight of normal testes among Caucasians. In Negroes whose external genitalia are usually more developed than those of White men, the testis itself tends to be somewhat smaller than the average for Caucasians.

Sexual Intercourse. — The histologic structure of the testis remains essentially normal in animals and men who have no sexual intercourse for very long periods. However, it has been observed that in the stallion it takes about 48 hours to produce the usual number of mature spermia, which are ejaculated in a single mating. Stallions mated several times a day produce immature and often non-motile, sterile spermatozoa. Conversely, if a stallion has not been mated for two months, the sperma also tends to be sterile, apparently because prolonged storage in the epididymis is harmful. Thanks to John Hammond's sustained interest in this matter we know, however, that a rabbit can copulate 39 times during 8 hours without a decline in fertility.

In man, after three to four successive intercourses, spermia are no longer demonstrable in the ejaculates. Sperm motility in vitro is preserved longest if the specimen is taken 2 to 3 days after the previous intercourse.

Season. — In animals having a limited breeding-season, the weight of the testis is largest during the period of mating. Thus in the sparrow, the average weight of the testis is about a thousand times greater in the Spring (the breeding season) than in Winter. Similar great variations in testis size have also been described in hibernating mammals.

There is no absolute parallelism between the seasonal development of the seminiferous epithelium and of the Leydig cells. The latter usually proliferate during the off-season, prior to spermatogenesis, presumably in order to permit the preparatory enlargement of the accessory sex organs, which must be completed when the mating season commences. Light appears to play a most important rôle in stimulating the secretion of the hypophysoid gonadotrophins necessary for the periodic testis development in such species. (See "Rays," on p. 642.)

In man, there is no manifest seasonal variation in testis structure.

Parabiosis. — Parabiotic union between a normal female and male rat causes testis involution, probably because the ovarian hormones inhibit gonadotrophin secretion by the male's pituitary. Yet, this atrophy is rarely pronounced and there have been cases in which such a parabiotic union did not interfere with the maintenance of normal fertility and testis structure in the male twin.

Temperature. — It has been thought that the seasonal development of the testis in hibernating and other

animals is due to temperature changes. It was found, however, that in the duck, sparrow, etc., exposure to warm temperatures during the off-season did not initiate spermatogenesis. We know now that light is the most important factor in these species. (See below.)

Nevertheless, temperature also plays a significant rôle in the morphologic development of the testis. The male gonad of most species is normally exposed to the comparatively low scrotal temperature The involution of the seminiferous epithelium in spontaneously or artificially cryptorchid testes is usually attributed to the higher peritoneal temperature. In the dog and sheep, it has been possible to show that if the temperature of the scrotum is merely raised to that normally prevailing in the peritoneum (by a special heating apparatus placed around the scrotum), the seminiferous epithelium undergoes the same changes as are usually seen in cryptorchid testes. Conversely, tubular degeneration can be prevented in cryptorchid testes if they are fixed on the peritoneum of the anterior abdominal wall and cooled by a special apparatus applied to the skin above them.

In man, heat is likewise detrimental for the seminiferous tubules; fever and exposure to high surrounding temperatures (e.g., in stokers) cause testis involution It is difficult to estimate, however, to what extent heat merely acts as a non-specific damaging agent, capable of eliciting a general-adaptation-syndrome with the consequent decrease in gonadotrophin production. Yet, in a patient in whom one testis was removed after local application of warmth to the scrotum, the seminiferous epithelium was also degenerated, although this intervention could hardly have caused any systemic damage. Human spermia may recover after freezing for 10 hours or even after immersion into liquid gases having a very low temperature. Apparently the spermia are much more resistant to temperature variations in vitro than in vivo.

Muscular Work. — *In certain birds* (e.g., Junco hyemalis), the normally seasonal enlargement of the testis may be elicited almost at any time by forced muscular exercise. Since this was believed to be so even in birds maintained in complete darkness, the effect of light was merely ascribed to this improved opportunity for muscular exercise in well-lighted surroundings (*Rowan*). However, in the duck, it could be shown that immobilization does not prevent the testis-stimulating effect of artificial illumination and it is generally agreed that even if muscular exercise in itself could exert some effect upon the testis, its seasonal development is chiefly due to increased illumination.

Rays. — The important effect of LIGHT RAYS, upon testis development in animals with a limited breeding season, has already been discussed in other connections. Suffice it to summarize the most important relevant facts as follows :

In birds (e g., duck, starling, junco, sparrow, green-finch), the development of the testis during the breeding season is inhibited by darkness. Conversely, testis growth may be obtained in the off-season by exposure to light. The orange and red parts of the spectrum are most active in this respect. Direct illumination of the optic nerve after enucleation of the eye-balls, or direct application of light to the optic nerve tracts, hypothalamus, or pituitary, likewise produces testis development, presumably as a result of increased gonadotrophin production.

In mammals, this action of light is absent, or at least less conspicuous. In the ferret (putorius vulgaris), artificial illumination elicits pronounced gonadal development only in the female; in the male the Leydig cells and the accessory sex organs are more readily stimulated than the seminiferous epithelium (*Bissonnette*).



X-Ray damage of testis. Testis of a man who was exposed to excessive roentgen irradiation. Absence of spermatogenesis and hyalinization of the seminiferous tubules which contained only Sertoli cells. The Leydig cells in the interstitial tissue are still well-preserved (Courtesy of Dr W Boyd)

X-RAYS AND RADIUM RAYS cause very pronounced involution of the spermatogenic epithelium, especially following direct exposure of the testis region The Leydig cells are much more resistant If small doses of X-rays are employed, the consequent testis-involution and sterility are merely transitory. Heavy X-ray treatment, however, causes permanent sterility in man and in animals

LOCAL TRAUMA may elicit neoplastic growth in the testes of certain birds (e g, fowl). Actual tumors resembling seminomas or teratoids have thus been produced by direct trauma to the testis or injection of a 5% zinc chloride solution.

It is of practical importance to remember that even in man such tumorigenesis may perhaps be elicited by local trauma In one series of 65 malignant tumors developing after orchidopexy, there were 34 unicellular and 19 teratoid tumors, while the remaining 12 instances were miscellaneous, or not definitely classified, testicular neoplasms

Other Agents. — A number of damaging agents (decreased atmospheric pressure, captivity (in wild animals), hemorrhage, burns, traumatic shock, drugs, etc.) cause testis involution, but merely in proportion to their general, non-specific damaging effect In all these cases, it is probable that we are merely dealing with one of the characteristic manifestations of the general-adaptation-syndrome, rather than with specific actions

DISEASES OF THE TESTIS

MALFORMATIONS

Among the malformations of the testis, those which tend to give rise to hormonal disturbances (aplasia, hypoplasia, true hermaphroditism and cryptorchidism) will be discussed in connection with the corresponding clinical syndromes (See. pp 645-666)

Among the malformations which are usually not accompanied by hormonal derangements, suffice it to mention UNILATERAL APLASIA, the formation of SUPERNUMERARY, OR ACCESSORY TESTES, the partial SEPARATION of a portion from

the main body of the gonad and FUSION of the testes. All these are extraordinarily rare anomalies.

ABNORMAL DESCENT ("*descensus aberrans*") may result in testes situated within the inguinal canal, the femoral canal or under the skin of the back of the penis. In the common type of *cryptorchidism*, the testis merely becomes arrested at some point during its physiologic descent from the kidney region into the scrotum (See: "Cryptorchidism," p. 648.)

Sometimes, there is a cross-over of the left testis to the right scrotum and vice versa (*descensus paradoxus*"). This may take place within the pelvis ("*dystopia transversa interna*") in which case the gonads traverse the contralateral inguinal canal, or externally ("*dystopia transversa externa*") when, after passing through the homolateral inguinal canal, the testes cross over to the contralateral scrotal pouch under the skin of the dorsum penis

Occasionally, ACCESSORY SPLENIC or ADRENAL-CORTICAL TISSUE islets are found in the testis region

ATROPHY, HYPERTROPHY AND HYPERPLASIA

ATROPHY of the testes is a comparatively common condition It can be due to systemic or local causes The *systemic-type of testis atrophy* is almost invariably the result of anterior-pituitary failure This may be caused by a primary disease of the pituitary itself, or by a secondary decrease in hypophyseal gonadotrophin production due to the development of a general-adaptation-syndrome. The testis atrophy seen in starvation, chronic infections (e g , tuberculosis) or prolonged mental strain is almost certainly due to a diminution of gonadotrophin production under conditions of stress which call for an increased elaboration of adrenotrophic and perhaps also of other metabolism-influencing anterior-lobe hormones.

Liver cirrhosis (e.g., in alcoholism or bronze diabetes) is especially frequently accompanied by severe testis atrophy, sometimes in conjunction with gynecomastia. The mechanism through which this syndrome is produced has not yet been elucidated, but the rôle played by hepatic detoxification of steroid hormones may be important in the pathogenesis of these conditions (see: p 79).

Among the agents which can elicit *testis atrophy by direct action* upon the gonad are: cryptorchidism, heat, X-rays, infections with local foci in the testis (orchitis) and sclerosis of the testicular vessels (especially in old people).

In general, it may be said that the spermatogenic cells, especially in their mature stages, are most sensitive, while the Sertoli and Leydig cells are least sensitive, to the various agents which cause testis atrophy. The resistance of these latter elements is particularly obvious if the testis atrophy is due to cryptorchidism or X-ray treatment, but even in liver cirrhosis, the Sertoli and Leydig cells tend to persist for a long time. On the other hand, hypophyseal failure affects both the Leydig and seminiferous cells, but is least damaging to the Sertoli cells.

HYPERTROPHY and HYPERPLASIA of the testis are rare Even compensatory hypertrophy, after ablation of one gonad, is never pronounced in the testis Isolated hyperplasia of the Leydig cells may result secondarily, due to excessive gonadotrophin production (chorionepitheliomas, anterior-pituitary tumors).

HEMORRHAGES AND OTHER VASCULAR LESIONS

HEMORRHAGES are especially frequent in the testes of newborn infants (due to trauma during delivery), but

may also occur as a result of torsion of the testis-pedicle, thrombosis and other vascular lesions.

Various generalized vascular diseases such as ARTERIOSCLEROSIS or PERIARTERITIS NODOSA can also affect the testicular vessels.

DEGENERATIONS

During the process of involution, abnormal, usually polynuclear, giant-cells are formed from the DEGENERATING SPERMATOGENIC EPITHELIUM (spermatogonia ?); these tend to undergo first HYALINIZATION and later even CALCIFICATION. The resulting CONCRETIONS are usually of small size and situated within the testicular tubules They are not rare and occur with particular frequency in *hypoplastic or atrophic* testes.

Other degenerative lesions (e.g., AMYLOID or GLYCOGEN *deposition*) in the testis are rare.

INFLAMMATIONS

A number of *infectious* diseases may lead to orchitis, due to the local development of inflammatory foci. Among these, tuberculosis, syphilis and mumps are particularly common. Gonorrhea tends to produce orchitis through ascension of the infection along the excretory passages. The so-called "traumatic orchitis" is probably always the result of a decrease in the resistance of the traumatized testis tissue to latent infections

MALE HYPOGONADISM

DEFINITION

Male hypogonadism is a condition in which the hormone-producing or spermatogenic function of the testis is disturbed

Depending upon the *patient's age* at the time of onset, and upon the quality and intensity of the underlying testicular lesions, hypogonadism manifests *itself in various forms For the sake of* simplicity these will be discussed conjointly, especially since, in many instances, both the hormone and the sperm production of the testis are *simultaneously* affected

CLASSIFICATION

The clinical types of male hypogonadism may be classified according to various points of view.

According to the AGE OF ONSET, we distinguish between

(1) *Early hypogonadism*, in which the onset is prepubertal.

(2) *Late hypogonadism*, in which the condition develops *during the normal* span of reproductive life

(3) *The male climacteric*, which usually commences at the end of the normal reproductive period.

This classification is justified, *because* the severity of the manifestations is inversely proportional to the age of the patient at the time hypogonadism makes its appearance

As regards the INTENSITY OF THE ENDOCRINE DEFICIENCY it is *customary to differentiate*

(1) *Eunuchism*, in which testicular hormones are completely absent, due *to aplasia*, surgical removal or destruction of the testis by disease

(2) *Eunuchoidism*, in which testis hormone production is merely diminished, but not *absent*

According to QUALITATIVE DIFFERENCES IN THE TESTICULAR LESIONS, it is customary to differentiate between ·

(1) *Destruction of both seminiferous and Leydig cell elements*

(2) *Isolated damage to the seminiferous tubules*, with normal Leydig cells.

(3) *Isolated damage to the Leydig cells*, with normal seminiferous tubules.

(This condition does not occur spontaneously, but has been produced experimentally in animals.)

It is obvious that all these classifications overlap, and indeed, it must be admitted that a completely satisfactory systematization of hypogonadism is still impossible because of our ignorance of the underlying etiologic mechanisms in many pertinent cases.

For didactic reasons, we have adopted the classification, illustrated in the adjacent table, which also lists the main characteristics of each type of hypogonadism. In the present section, we shall merely enumerate the chief manifestations of these diseases which permit us to delimit them from each other. Details concerning the clinical symptomatology of the various types will be discussed conjointly later (see· Clinical Course, p. 650 and Diagnosis, p. 663), in order to facilitate comparisons between the effects of the divers forms of hypogonadism on each target organ.

(1) EARLY EUNUCHISM. — This type of hypogonadism is due to complete testicular deficiency (aplasia, surgical castration, destruction of both testes by disease) developing at an early age, always before puberty. It leads to the most pronounced disturbances in the development of all MALE SEX CHARACTERISTICS. The severity of the disturbance is mainly due to the fact that testicular deficiency occurs before the morphogenesis of the organs has proceeded far enough to give them a definitely male character The testes are absent, the penis and other accessory sex organs are extremely hypoplastic. There is a great tendency to exaggerated GROWTH in length (especially of the extremities) and the general body configuration is more of the female type, with broad hips. Frequently, there is a great tendency towards OBESITY, especially of the breasts, hips and abdomen. LIBIDO and potentia are markedly diminished and often completely absent. The SKIN is delicate and almost free of lanugo hair. Pubic, axillary and facial hair growth is deficient, while the scalp hair is abundant and usually very fine. The VOICE retains its boyish quality, since the masculine development of the larynx is inhibited.

(2) LATE EUNUCHISM. — The appearance of individuals who lose their testes after puberty usually differs but little from that of normal adult males. There may be atrophy of the accessory sex organs, but libido and potentia are not necessarily abolished and all the above-mentioned characteristics of eunuchism are much less pronounced than in the early eunuch. This is particularly true of the bone development, which remains essentially normal if testicular failure began after completion of ossification in the junction cartilages.

(3) HYPERGONADOTROPHIC EUNUCHOIDISM WITHOUT A-LEYDIGISM (*Klinefelter et al.*). — Here the clinical manifestations (eunuchoid accessory sex characteristics, bone structure, etc) are intermediate between those characteristic of early and late eunuchism, respectively. This is due to the fact that although testicular insufficiently develops at an early age, it is not complete. The chief characteristics of this disease are · 1) absence of the seminiferous epithelium, with normal development of the Leydig cells; 2) approximately normal Sertoli cells, as long as the tubules are not completely obliterated; 3) usually normal 17-KS excretion, but high gonadotrophin content in the urine, such as is seen in castrates.

(4) EARLY HYPOGONADOTROPHIC EUNUCHOIDISM. — In this condition, the general aspect of the patient resembles that of the early eunuch. However, since here the gonadal deficiency is due to anterior-lobe failure, other manifestations of hypopituitarism (e.g. retardation of somatic growth, decrease in B.M.R.) are also manifest, unless the gonadotrophin production of the anterior-lobe is selectively damaged. The

Classification and Characteristics of Various Types of Male Hypogonadism

Disease		Clinical Characteristics				Testis Structure			Urinary hormone assays			Onset
		♂ accessories	Breasts	Bones	Muscular strength	Seminif epithelium	Sertoli cells	Leydig cells	Gonadotrophins	Testoids and/or 17-KS	Folliculoids	
Eunuchism	Early	—	+ or N	Eunuchoid	—	Absent	Absent	Absent	+ or N	—	— or N	prepubertal, usually caused by orchidectomy
	Late	— or N	+ or N	N	— or N	Absent	Absent	Absent	+	—	— or N	postpubertal, usually caused by orchidectomy
Eunuchoidism	Hypergonado-*trophic* without a-Leydigism (Klinefelter et al).	— or N	+	Eunuchoid or N	— or N	—	— or N	N	+	— or N	— or N	prepubertal, of unknown etiology
	Early Hypogonadotrophic [1]	—	N	Dwarfed or N	—	—	N	—	—	—	—	prepubertal, due *to anterior* pituitary failure
	Late Hypogonadotrophic	— or N	N	N	—	—	N	—	—	—	—	postpubertal, due to anterior pituitary failure
	Simple delayed puberty [1]	—	N	— or N	— or N	—	—	— or N	?	—	?	prepubertal, due to transitory anterior-*pituitary* failure
Sterility without Eunuchoidism	Cryptorchidism	— or N	+ or N	Eunuchoid or N	— or N	—	N	N	+	— or N	—	prepubertal, due *to malformation* or endocrine disturbances
	Aspermatogenic (or dysspermato-*genic*) with orthotopic testes	N	N	N	N	—	N	N	+	N	N	prepubertal or postpubertal, due to X-rays, *orchitis*, E-avitaminosis, etc
	Normo-spermatogenic	N	N	N	N	N	N	N	N	N	N	postpubertal, due to obstruc*tion* of seminiferous passages psychic impotency, etc
Male Climacteric		N	N	N	N	— or N	N	— *or* N	+	—	—	Spontaneously at 45-50, earlier after *postpubertal* castration

[1] *Often difficult to differentiate* from Fröhlich's syndrome, may be accompanied by cryptorchidism.

+ = *increase or* stimulation of development
— = decrease or inhibition of development
N = no change *(normal)*

seminiferous epithelium and the Leydig cells of the testis become atrophic, while the Sertoli cells tend to persist. The urinary elimination of gonadotrophins, 17-KS and folliculoids is low.

(5) LATE HYPOGONADOTROPHIC EUNUCHOIDISM — Here, the clinical manifestations, the testis morphology and the changes in hormone elimination are essentially similar though less severe than those of early hypogonadotrophic eunuchoidism.

(6) SIMPLE DELAYED PUBERTY. — *This condition is on the borderline of* the normal, since it is rather difficult to specify a certain age after which puberty must be regarded as abnormally delayed In many cases, boys do not enter the puberty period until about 17 years of age, yet subsequently their sexual development becomes normal. It is also difficult to delimit delayed puberty from certain types of Frohlich's syndrome and other types of anterior-lobe failure. Generally speaking, delayed puberty is characterized by infantilism of the accessory sex characteristics (sometimes accompanied by cryptorchidism), and often also of somatic development in general. The testes are immature, but otherwise essentially normal. There are comparatively few data concerning disturbances of hormone metabolism in this condition

(7) STERILITY WITHOUT EUNUCHOIDISM. — CRYPTORCHIDISM (or cryptorchism) is a condition in which one or both testes fail to descend into the scrotum, remaining in the abdominal cavity or in the inguinal canal. The unilateral form is much more common than the bilateral, but only the latter is necessarily conducive to sterility. Cryptorchidism may be due to merely mechanical obstruction of the passages through which testicular descent normally occurs, and then it is often unaccompanied by signs of eunuchoidism In other instances, however, it is the result of an endocrine deficiency, since hypophyseal and testoid hormones play important parts in the normal descent of the male gonad. (See: p. 650) In such cases the clinical manifestations will be largely those of the underlying type of eunuchoidism. Simple cryptorchidism (of non-hormonal origin) is not incompatible with the normal development of all accessory sex characteristics and the male differentiation of the soma. The seminiferous epithelium is always deficient or completely absent, however, since its cells fail to develop at the temperature prevailing in the abdominal cavity. The Sertoli and Leydig cells are normally developed and hormone production, as judged by male differentiation and 17-KS excretion, is rarely affected. Nevertheless, gonadotrophin elimination is high, perhaps because some pituitary inhibiting factor of the seminiferous cells ("inhibin") is lacking. — Only in cryptorchidism of very long standing is there Leydig cell damage.

ASPERMATOGENIC (OR DYSSPERMATOGENIC) STERILITY WITH ORTHOTOPIC TESTES is unaccompanied by signs of eunuchoidism and the only manifest abnormality is a deficient development, or complete absence of, the seminiferous epithelium. It may be due to orchitis, X-ray treatment of the testis or certain dietary deficiencies (e g., vitamin-E deficiency, to which the seminiferous cells are particularly sensitive) but in many instances, the past history of the patient reveals no event which could be of etiologic significance.

NORMO-SPERMATOGENIC STERILITY, that is, infertility in the absence of any detectable morphologic derangement in spermatogenesis, is unaccompanied by signs of eunuchoidism. It may be due to obstruction of the seminiferous passages, psychic impotence and a variety of other causes. We mention it here, merely for the sake of completeness, although there is no evidence that it is of hormonal origin

(8) THE MALE CLIMACTERIC. — While in the female, climacteric disturbances are comparatively common at the age of the menopause, this is but rarely the case in the male. Perhaps the much more gradual decline in the sexual functions of men, as compared with the abrupt cessation of sexual cyclicity in women, is responsible for the rarity of severe climacteric disturbances in males. This view is supported by the fact that castration, during the sexually active period of life, frequently elicits these manifestations in the male also.

The condition is characterized by essentially the same symptoms which we discussed in connection with the female climacteric, mainly vasomotor and psychic disturbances.

Testicular biopsies usually reveal a decrease in the development of the seminiferous epithelium and the Leydig cells

Hormone assays show an increase in urinary gonadotrophin with a decrease in 17-KS, active testoid and folliculoid hormone elimination.

It will be noted that in all conditions conducive to a decrease in the development of the seminiferous epithelium, the urinary gonadotrophin excretion (mainly FSH) is high, as long as there is no concomitant anterior-lobe failure. (See : *"Pathogenesis."*)

PATHOLOGIC ANATOMY

The testicular lesions characteristic of the various types of male hypogonadism, have been discussed above (See . "Classification" of hypogonadism, "Malformations" and "Inflammations" of the testis)

INCIDENCE

Delayed puberty, and even delayed descent of the testes into the scrotum, are comparatively common, but permanent cryptorchidism, eunuchism, hypergonadotrophic eunuchoidism without a-Leydigism (Klinefelter syndrome), and the various types of hypogonadotrophic eunuchoidism are rare conditions.

The most common types of male hypogonadism are the less severe derangements in sperm production and the male climacteric, but accurate statistical data concerning their incidence are not available as yet.

PATHOGENESIS

As previously stated, EUNUCHISM is almost invariably due to surgical removal of the testes (for tuberculosis, tumors, etc.). In ancient times, it was often performed for religious reasons (e.g., among the Skoptsi), as well as among the keepers of harems to give the owners a feeling of security — which, as we shall see (p. 661), was ill-founded.

Eunuchism decreases urinary testoid, 17-KS and folliculoid elimination, since it removes one of the most important sources of these compounds. The continued excretion, in small amounts, of such steroids in castrates, is probably attributable to adrenal-cortical secretion. On the other hand, the gonadotrophin production is augmented owing to the removal of testicular inhibitory influences.

In the various types of EUNUCHOIDISM, urinary gonadotrophin elimination rises, whenever the seminiferous epithelium is destroyed, irrespective of the presence or absence of Leydig cells. This observation led to the opinion that some hypothetic hormone ("inhibine ?"), produced by the seminiferous cells, is responsible for the inhibition, by the testes, of hypophyseal gonadotrophin formation Further work will be necessary to prove this point, although many facts speak in its favor. *In hypogonadotrophic eunuchoidism*, with simultaneous hypophyseal and testicular failure, this increase in the hypophyseal

gonadotrophin secretion is missing, since anterior-lobe failure is the primary cause of the deficiency in testis development.

The etiology of *hypergonadotrophic eunuchoidism without a-Leydigism (Klinefelter syndrome)* is still unknown, but probably the condition is (as many instances of cryptorchidism) due to derangements of sex differentiation during embryonic, or early postnatal life.

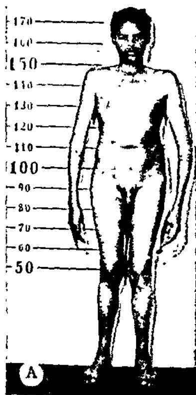
The various types of ASPERMATOGENIC OR DYSSPERMATOGENIC STERILITY WITHOUT EUNUCHOIDISM are due to X-rays, orchitis, vitamin-E deficiency and various other agents specifically destructive to the seminiferous cells. It must also be kept in mind however that the spermatogenic epithelium is particularly sensitive to gonadotrophin deficiency, hence it is the first to suffer from any diminution in anterior-pituitary gonadotrophic hormone production, such as occurs under the influence of various types of stress. Only severe and continuous non-specific damage (diabetes mellitus, myxedema, chronic undernourishment) especially if it commences before puberty, damages the Leydig cells sufficiently to cause hypogonadotrophic eunuchoidism

As previously stated, CRYPTORCHIDISM is often due to mechanical obstruction of the inguinal canal In other instances it is caused by a hormonal derangement, such as lack of gonadotrophins, with the resultant chain of events, including testicular hypoplasia, deficiency in testoids, hypoplasia of the scrotum and deficient shrinkage of the gubernaculum testis, which normally pulls the gonad downwards. The development of the scrotum certainly plays an important rôle in the pathogenesis of cryptorchidism. It is noteworthy that in animals, whose inguinal canal remains open throughout life (e.g., rat), any intervention which diminishes testoid production (e.g., folliculoid treatment, hypophysectomy) causes secondary cryptorchidism, due to a permanent return of the testes from the scrotum into the peritoneal cavity. This is prevented by adequate treatment with testoids, which maintain the size of the scrotum. Conversely, in male castrates, testoid therapy in itself does not suffice to maintain the development of the scrotum, since the mechanical presence of the testes is also necessary. If, on the other hand, glass balls are inserted into the scrotum of testoid-treated castrate male rats, the scrotum is maintained, due to the combined action of mechanical distention and hormone action. In other words the scrotum-enlarging effect of testoids is conditional and dependent upon mechanical distention of the scrotal sac.

The disturbances of the male CLIMACTERIC are probably due to an abrupt decline in the endocrine functions of the testis. That is perhaps why they are so frequent after castration, while in aging men, this decline is rarely so sudden as to elicit serious climacteric symptoms. Even if such are manifest, however, the testicular failure is hardly due to a decrease in anterior-hypophyseal function since gonadotrophin elimination is often increased.

CLINICAL COURSE

State. — Hypogonadism does not seriously influence the GENERAL RESISTANCE of the patient, except when the testicular failure is secondary to a hypophyseal lesion In this event, the great increase in sensitivity to various types of stress (infections, intoxications, etc.) characteristic of anterior-lobe deficiency, becomes manifest The poor development of the muscular system in eunuchs and eunuchoids (see p 660) is responsible for their low resistance to any type of muscular stress, irrespective of the etiology of

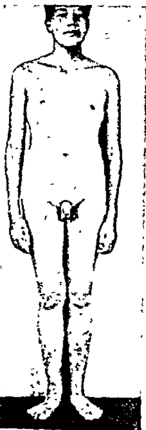




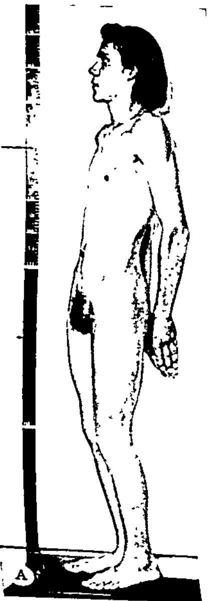
Eunuchoidism — A. Adult Negro with deficient genitals and hair development, eunuchoid body proportions and feminine facies. Urine was practically free of gonadotrophins and 17-KS — B. Note atrophic testes and absence of pubic hair in same patient (Courtesy of Dr J I Lobo)

the hypogonadism. Sometimes secondary nutritional factors, especially anorexia nervosa or excessive adiposity, further impair the resistance of these patients.

The FACIAL EXPRESSION, especially of early eunuchs, is characterized by a mixture of infantile (lack of beard growth, undifferentiated facial bone structure) and senile (tired facial expression, early development of fine wrinkles, yellowish waxy skin color) traits. Even if they spend most of their time outdoors, they do not tend to show the effects that sun and wind exert upon the facial aspect of normal individuals A slight tendency towards ptosis of the upper eyelids often gives them a tired expression, which sometimes changes to that of surprise since they have to wrinkle the skin of their forehead to open the palpebral fissures The root of the nose is frequently depressed ("saddle nose").

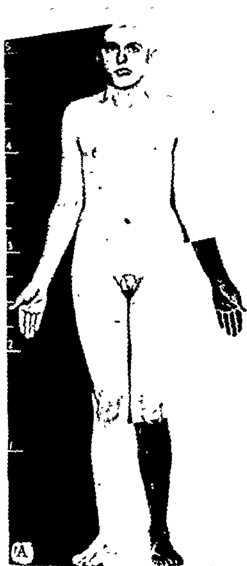


Eunuchoidism 23 - year - old Japanese with subnormal genital development absence of pubic and axillary hair and disproportionately long extremities (Courtesy of Dr J I Lobo)






Pseudohermaphroditism in a male. — A 18-year-old 'woman' admitted for primary amenorrhea. There was a palpable tumor in the left inguino-abdominal region (testis). The right gonad (testis?) was removed under the diagnosis of hernia two years earlier. Hypospadias and male libido. — B Note masculine aspect of genital organs. — C Biopsy specimen of testis removed during surgical fixation in the scrotum. Note that tubules contain only Sertoli elements but Leydig cells are well-developed. — D High magnification of C.
(Courtesy of Dr E B del Castillo.)



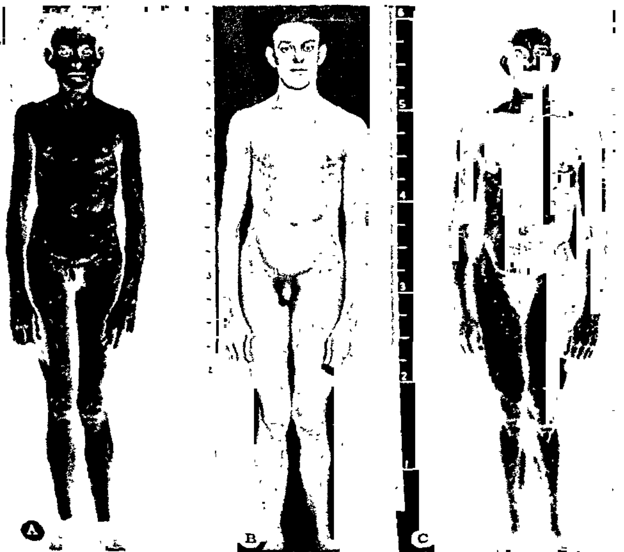


Hypogonadism with multiple congenital anomalies. — A. 21-year-old patient with eunuchoidism. Appearance of maturity and general development approximately that of a 12-13-year-old boy. Height 63", weight 120 lbs., sella normal to X-rays, urinary FSH 6-105 M.U./24 hrs., 17-KS 3.1 mg./24 hrs. There was microphthalmia, bilateral coloboma, right facial weakness, high arched right palate, bifid uvula and loud systolic murmur at left of sternum, probably due to congenital cardiac defect. — B. Testis biopsy showing deficient development both of tubular and interstitial cells. The etiology of this type of eunuchoidism is not known.
(Courtesy of Dr. E. P. McCullagh.)





Unilateral Pseudocryptorchidism. — A. Adult man in whom one testis failed to descend but was palpable in the inguinal canal. Note also absence of pubic hair. — B. Same patient one year and eight months later after having received a total of 340 mg. of testosterone proprionate. The right testis is now in the scrotum and pubic hair has developed.
(Courtesy of Dr. J. J. Lobo.)

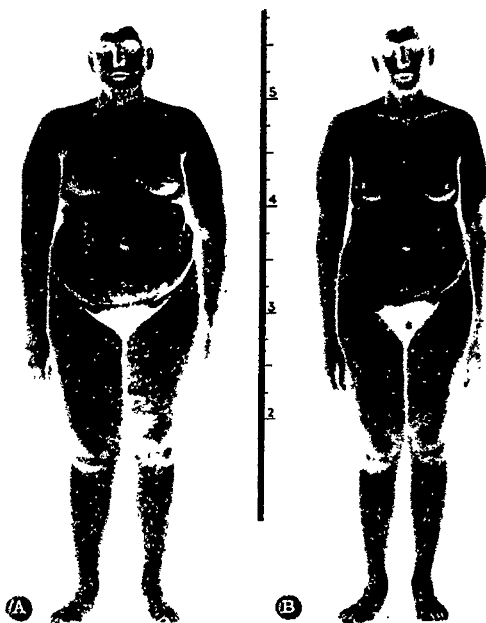


Therapy of eunuchoidism with *testosterone.* — A. Severe eunuchoidism *following testicular* atrophy caused by an attempted bilateral orchidopexy for cryptorchism, appearance of patient at the age of 23 years before testosterone therapy — B. Following *intermittent testosterone therapy* during four years — C. Following ten years *of testosterone therapy,* note *striking* increase in sexual maturity, facial maturity *and growth* of skeletal *musculature* (Cont'd on page 655)



— D. The gracile hand in severe eunuchoidism (left) as compared with the hand of a normal man — E. Facial acne during intensive testosterone therapy — F. Gynecomastia following 3 months of intensive methyl-testosterone therapy

(Courtesy of Dr E P McCullagh)

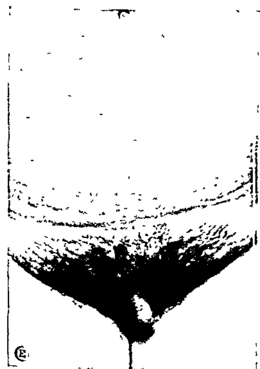


Eunuchoidism. Age 31 years, height 71½", arm span 77½", weight 264 lbs Bilateral gynecomastia, hairline not receded, face beardless, arms and legs relatively hairless, axillary hair scarce, pubic hair of female distribution, penis smaller than average, testes pea-sized, prostate very small, voice high-pitched, ... normal, B.M.R. —2%, 17-KS 8 6 mg /24 hour ... and E show the patient before, B, D and F, ... oses of 25 mg thrice weekly ...

(Courtesy of Dr E P McCullagh)


C


D


E


F





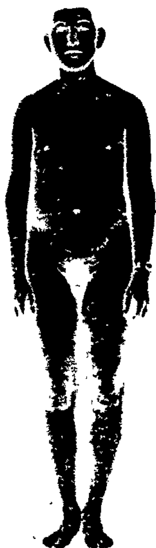


Cryptorchidism — A. Cryptorchid testis of an adult m ... lined on ... a dense ... are well ... epithelıur ... of the stı ... dıg cell proliferation in the stroma of the above testis Note one atrophic seminiferous tubule within the Leydig cell islet — C. A group of Leydig cells with typical Reinke crystalloids between atrophic tubules whose thick, hyalinized, basement membrane is clearly visible at this magnification The Sertoli cells are well-developed, but somewhat irregular in shape, due to absence of spermatogenic elements around them

(Courtesy of Dr W. Bonio)

A TODDLING WALK (due to flat-feet, knock-knees and muscular weakness) is likewise very characteristic of hypotestoidism acquired during early childhood.

Metabolism.— The B.M.R. is usually low and there is a tendency towards creatinuria, with a diminution of PROTEIN anabolic processes Otherwise, the metabolic changes in hypogonadal



Eunuchoidism. Age 27 years, facial appearance puerile, voice high-pitched, no beard (except a few scattered hairs on chin), axillary and pubic hair approximately half of normal arms and legs relatively hairless, prostate about ⅓ to ½ normal, testes very small 17-KS excretion 6 6 mg /24 hrs, urinary FSH excessively high (105-212 M.U /24 hrs repeatedly)
(Courtesy of Dr E.-P McCullagh)

individuals are not very prominent Treatment with testosterone and its esters, unlike methyl-testosterone, decrease creatine and total nitrogen excretion.

The very tall patients are usually lean, while excessive FAT DEPOSITION is particularly common among the shorter individuals, although this is not an absolute rule. In the adipose type, fat deposition is particularly prominent about the buttocks, thighs, mons veneris, lower abdomen and breasts. Testoid therapy tends to correct this type of adiposity.

The derangements in HORMONE METABOLISM differ in the various forms of hypogonadism (see: pp. 628, 629, 647).

Growth and Bone Structure. — The most prominent skeletal abnormalities in individuals in whom testicular failure developed before puberty are · excessive growth of the extremities, as compared to the trunk and head; narrowness of the hands and feet, with great elongation of fingers and toes, especially of the thumb and large toe; infantile (asexual) configuration of the pelvis; delay in the ossification of the junction cartilages (probably chiefly responsible for the excessive growth in length) and a tendency towards the formation of genu valgum and flat-feet. Early testoid therapy prevents these skeletal anomalies.

Cardiovascular System. — The BLOOD PRESSURE of eunuchs and eunuchoids is usually low, the PULSE-RATE tends to be slow and the CARDIOVASCULAR APPARATUS hypoplastic. This adds to their great fatigability. Their *characteristic pallor is due to inadequate* cutaneous blood supply.

HOT FLUSHES, often followed by sweating, are most common in postpubertal eunuchs, especially during the period immediately following orchidectomy; these respond well to testoid treatment

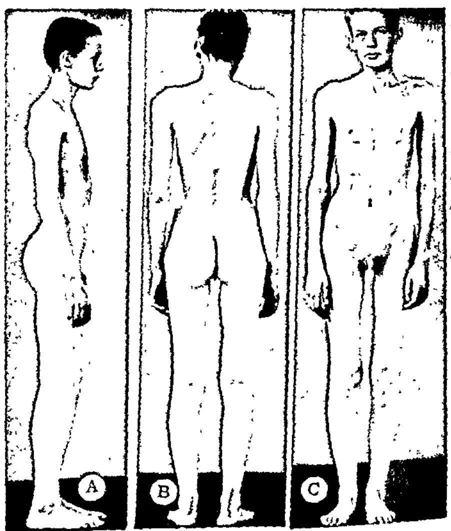
Lymphatic System. — The thymus, spleen and lymph nodes of eunuchs and eunuchoids tend to be very well developed, due to the deficiency of testicular, testoid and folliculoid hormones, which are known to promote involution of the lymphatic system.

Respiratory System. — The development of the larynx is deficient, but

only if the onset of eunuchism or eunuchoidism precedes puberty. In such patients, the larynx is small, and the angle of the thyroid-cartilage plates is blunt, so that the "Adam's apple," characteristic of the adult male, is not prominent. The ossification of the laryngeal cartilages fails to occur. As a result of these changes, both the anatomic configuration of the larynx and the vocal pitch remain of the prepubertal type throughout life. Early administration of testoids permits the normal and irreversible masculinization of the larynx in eunuchs and eunuchoids.

Muscles. — The muscles of eunuchs and eunuchoids are poorly developed, flabby, and often infiltrated with fat. Consequently their strength is usually far below normal. Testosterone and its esters stimulate muscular development in such patients while methyltestosterone is of questionable value.

Nervous System. — All types of hypogonadism tend to be associated with more or less severe PSYCHIC DISTURBANCES. It is very difficult to establish, however, which of these are the direct result of the hormonal insufficiency and which are secondary to the



Primary hypotestoidism. — A, B and C. Primary hypogonadism of unknown etiology. Note lack of pubic hair, atrophic genitals and disproportionately long extremities. (After W. M. Yater: Fundamentals of Internal Medicine. — Appleton Century Publ. 1944.)

psychic trauma suffered by patients who resent their inferiority and suffer from *the hostility and ridicule with* which they are received by the society in which they live. In general, eunuchs tend to be lacking in initiative and fighting spirit. They are often hypochondriacal, introverted, shy and they frequently seek the protection of other people. Many of them become sullen, *untrustworthy, and develop schizophrenic* traits.

During the male climacteric, general nervousness, insomnia, irritability, incapacity for mental concentration and nervous depression with severe inferiority complexes, anti-social and even suicidal tendencies may become prominent.

Libido and potentia are usually diminished and frequently absent, but in patients in whom erections are sufficient to permit the sexual act, orgasm may occur, even in the presence of complete eunuchism.

Testoid hormone therapy is often very effective in correcting all these psychic derangements.

Digestive System. — Male hypogonadism does not tend to produce any characteristic changes in the gastrointestinal tract. The cause of the comparatively frequent association of liver cirrhosis, gynecomastia and eunuchoidism is not fully understood (see p. 644).

Skin and Appendages. — The skin of eunuchs and eunuchoids is characteristically parchment-like or pasty and sallow, due to poor blood supply, lack of melanin and perhaps also an increase in carotenoid pigments Superficially, it looks like the skin of a child, because of the *absence of deep furrows, but on* closer inspection, innumerable, extremely fine wrinkles are usually detectable in the delicate integument, even in comparatively young adults. Since SEBACEOUS SECRETION is diminished, the skin and hair are dry The sebaceous glands are atrophic and acne does not occur in these individuals. The beard and mustache of eunuchs and eunuch*oids resembles that of adolescents in* that they consist only of a few, lanugo-like HAIRS. The axillary and pubic hair is likewise scanty and of very fine texture The pubic hair line is of the female type inasmuch as it does not extend towards the umbilicus. The lanugo on the trunk, limbs and eyebrows *is also extremely fine and sparse* The scalp hair is extraordinarily dense and of silky texture. Early eunuchs and eunuchoids do not become bald, and indeed the hair line tends to extend downwards over each temple, well towards the lateral edge of the eyebrow, as it does in women.

All these changes are especially prominent if hypogonadism preceded the onset of puberty In postpubertal eunuchs, beard and pubic hair growth may remain normal throughout life Hair growth on the scalp is rarely induced by postpubertal castration in bald patients, but conversely, the administration of testoids may elicit apical baldness with beard, mustache, eyebrow and body hair growth in prepubertal eunuchs and eunuchoids In late castrates who had acne at puberty, this tends to reappear every time testoids are given

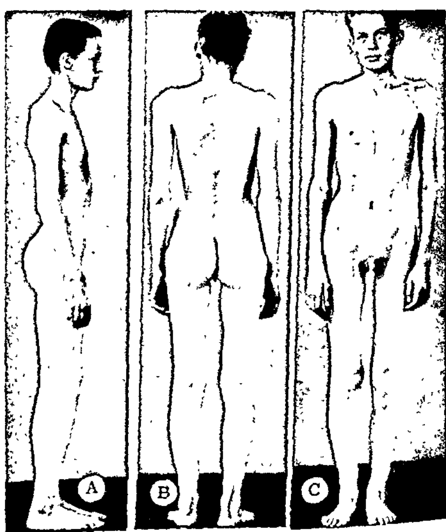
Urinary System. — The kidneys of eunuchs are frequently small

Accessory Genital Organs. — In eunuchoids and especially in eunuchs, the size of the PENIS, EPIDIDYMIS, SEMINAL VESICLES, PREPUTIAL GLANDS AND COWPER'S GLANDS is considerably subnormal and the PROSTATE may hardly be palpable by rectal examination. Due to the narrowness of the excretory pas*sages the urine stream is thin and feeble* Nevertheless more or less complete erections and even sexual intercourse may be possible some years after orchidectomy, although in such instances, the ejaculate is subnormal in amount and of aqueous consistency It is noteworthy that for several days after orchidec-

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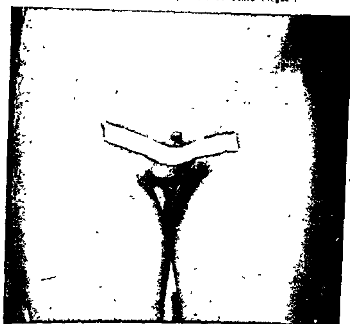
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Cryptorchidism. Note absence of the testes in the scrotum of this adolescent boy
(Courtesy of Dr A Pinto Viégas)



(Courtesy of Dr A Pinto Viégas)



Hypotestoidism with cryptorchidism. — 16-year-old boy with small penis, absence of pubic hair testes not palpable in scrotum or inguinal canal (Courtesy of Dr J J Lobo)



tomy, fertile intercourse remains possible, owing to the prolonged life-span of the spermia in the sexual passages. The SCROTUM is small, lacking in pigment and wrinkles, with an almost indistinguishable raphe, especially in early eunuchs. In postpubertally castrated men, the accessory sex organs tend to remain fairly large.

In eunuchoids, the size of the TESTES is considerably subnormal and the gonads are often cryptorchid or at least retracted in the direction of the external inguinal canal.

Fertility. — All types of eunuchism and eunuchoidism are conducive to sterility, although in certain cases of dysspermatogenic hypogonadism fertility may be merely impaired, not abolished.

DIAGNOSIS

In fully developed cases of eunuchism or eunuchoidism, the diagnosis rarely causes difficulties, since the clin-

Gynecomastia without aspermia. — A and B. Age 25 years, height 73½", weight 236 lbs genitalia normal, sperm count 157 millions (85% motile with 3-4 plus motility) urinary FSH 53-105 M.U./24 hrs. Testis biopsy shows active spermatogenesis, breasts consist of abundant fibrous tissue and fat, with occasional ducts. *(Courtesy of Dr. E. P. McCullagh.)*



ical manifestations (see: Clinical Course) are very characteristic. Punch biopsies of the testis, morphologic examination of the ejaculate, and urinary hormone analyses are of special value in determining the specific type of hypogonadism from which the patient suffers. The features characteristic of each type of hypogonadism have been summarized under "Classification" (pp. 645-649).

For the diagnosis of CRYPTORCHIDISM, it is of particular importance to exclude "pseudocryptorchidism," in which the testes have descended but remain migratory, moving up and down spontaneously from the scrotum high into the region of the inguinal canal. In these cases, the local application of heat, to relax the muscles, and pressure over the external inguinal ring help to move the testes into the scrotum Some investigators recommend a therapeutic test with gonadotrophins to determine whether cryptorchidism is due to mechanical obstruction (correctable only by surgery) or to a hormonal deficiency.

Examination of the sperm is especially important in the diagnosis of STERILITY The ejaculate can be obtained by masturbation or coitus interruptus, not in condoms, since these are usually treated with substances which damage the spermia. The specimen is collected in a clean glass bottle and may be kept at warm room temperature (e.g., in an inner pocket) for 1-2 hours before examination, by which time the originally clotted material liquefies again The main characteristics for which the specimen should be examined are ·

(1) *Volume*. This is usually 3-4 cc.

(2) *Physical characteristics*, such as undue discoloration, abnormal density, or deviation from the normal alkaline reaction.

(3) *Motility*. The percentage of motile spermatozoa is estimated in seminal fluid examined by the "hanging drop" method. Normally, 80-95% of the spermatozoa are active. Only direct forward locomotion can be regarded as normal motility; rotary or pendulum swinging is not. It is also noteworthy that motility decreases in specimens kept in vitro too long.

(4) *Count*. The sperm count ranges between 60 and 100 millions per cc but may be even greater than this. It is usually determined in a leukocyte or erythrocyte pipette using 5% sodium bicarbonate, with 1% formalin as a diluting fluid. The specimen must be well shaken before counting to insure equal distribution.

(5) *Morphologic characteristics of the spermatozoa*. These are usually studied on suitably stained smears Normally, there should be less than 20% abnormal forms, that is, immature or necrotic forms, spermia with giant, pin, pyriform, narrow or double head, bent or thickened neck, coiled, double or absent tail, etc.

(6) *Spermatozoal endurance*. This is tested by placing semen specimens in three sealed test tubes, kept respectively · 1) at room temperature, 2) in a refrigerator and 3) in an incubator (at 37°C). By examining the motility of the specimens in the hanging drop preparation at hourly intervals, the endurance of the spermia is tested. Motility increases but the life span of the spermia decreases in proportion with the temperature Normally, at room temperature they should remain motile for at least 6 hours.

Testicular Biopsy is a very simple diagnostic intervention, useful in the recognition of various types of hypogonadism It is usually performed as follows: After local anesthesia of the overlying scrotum and antiseptic preparation of the skin, the testis is pressed tightly against the scrotum and exposed through a skin incision of about 1.5 cm. Subsequently a minute stab-wound is made with a pointed lancet in the testis capsule and a small amount

of white testicular parenchyme is squeezed out by gentle pressure and fixed for *histologic examination*. A single stitch suffices to close the scrotal incision, while the testis capsule heals without suture. Some physicians prefer the "punch biopsy" method, in which a special instrument is used. Both technics are essentially similar and extremely simple; they do not inconvenience the patient for more than an hour or two.

PROGNOSIS

Delayed puberty and certain types of cryptorchidism and hypogonadism, due to temporary anterior-lobe failure, may regress spontaneously or after elimination of the underlying etiologic agent (e.g., nutritional deficiencies, chronic metabolic diseases). In other instances, gonadotrophic or testoid therapy proved of great value, while psychogenic impotence should respond to appropriate psychotherapy. The disturbances of the male climacteric tend to vanish after the critical age

THERAPY

In connection with the treatment of male hypogonadism, we must distinguish between the therapy of:

(1) Hypotestoidism.
(2) Cryptorchidism.
(3) Sterility.

HYPOTESTOIDISM (eunuchism or *eunuchoidism*), *should be treated with* testoid hormones, in agreement with the principles outlined in the section concerning their pharmacology.

Transplantation of testis tissue would appear to be the most logical therapy of eunuchism, but only human grafts have a reasonable chance of success and even these tend to involute after some time. However such transplants do not restore fertility in any case and since testoid therapy is more likely to be effective, the latter is generally preferred.

In eunuchism, only testoid therapy can be efficient, since there is no testis *tissue which could be stimulated by* gonadotrophins If puberty antedates the onset of hypotestoidism, continuous testoid treatment may permanently *maintain development of the accessory* sex organs and potentia. Otherwise the efficacy of this therapy is usually more limited, although some degree of growth of the penis and other accessory sex organs is almost invariably elicited by testoids, the hair distribution tends to assume a more masculine type, and the voice deepens.

In hypogonadotrophic hypogonadism, the administration of gonadotrophins is often successful, though not invariably, perhaps because the sensitivity of the testis tissue is diminished.

CRYPTORCHIDISM due to mechanical obstruction of the inguinal canal responds only to surgical therapy, but if the condition is due to anterior-lobe failure, gonadotrophins (100-6,000 I.U of LH given three times a week) may be effective, especially in combination with testoids. However, this treatment is usually ineffective if instituted after *the 15th year of age, and in younger* boys the possibility of a spontaneous cure is difficult to eliminate. In view of the frequent spontaneous correction *of cryptorchidism, initiation of any therapeutic measures before the 13th-*15th year is not recommended.

Pseudocryptorchidism also tends to *respond to gonadotrophic hormones,* especially in combination with testoids which promote the growth of the scrotal sac, although this condition *frequently corrects itself spontaneously.*

The value of general therapeutic measures such as the reduction of the food intake in adipose boys, the provision *of an adequate caloric* and vitamin intake in undernourished patients, etc., must likewise not be neglected.

In the treatment of STERILITY, due to isolated failure of the spermatogenic

epithelium, the administration of gonadotrophins and testoids is recommended, although by no means uniformly effective. Theoretically, the best procedure would be the administration of a highly active spermatogenic steroid or anterior-lobe extract (e.g., pregnenole or FSH). However none of the preparations now on the market have proven to be of consistent efficacy.

In special instances, the rational etiologic therapy of the underlying condition gives the best results. Thus in sterility due to hypothyroidism, thyroid hormone, in that caused by hyperthyroidism, surgical or internal therapy of this latter condition are often effective: in other instances, the administration of a balanced diet containing the necessary essential amino-acids and vitamins, the avoidance of physical fatigue or nervous exhaustion, as well as prolonged sexual abstinence with intercourse only during the fertile phase of the female cycle, are advisable. If sterility is due to an obstruction of the epididymis, fertility can sometimes be restored by a surgical intervention uniting the vas deferens with the head or body of the epididymis. This intervention should only be performed, however, after having established, by punch biopsy, that the testis can produce normal spermatozoa.

HYPOGONADISM IN ANIMALS

The various types of hypogonadism which occur in man may also develop, spontaneously, in animals. It is not within the scope of this book to discuss these in detail, but we wish to emphasize the great practical importance of sterility and its management (hormone therapy, artificial insemination, etc.) among valuable pure-bred domestic animals.

Spontaneous cryptorchidism is especially common in pigs. If bilateral, it invariably causes sterility, but rarely signs of hypotestoidism.

MALE HYPERGONADISM

DEFINITION

The term male hypergonadism comprises conditions in which the hormone-producing, the spermatogenic function, or both these activities of the testes are excessive.

For the sake of simplicity in the present section, these conditions will be discussed conjointly. The testicular neoplasms conducive to excess production of gonadotrophins or corticoids, and those unassociated with endocrine disturbances will be discussed separately. (See: "Testis Tumors in General," p. 672.)

CLASSIFICATION

It is customary to classify male hypergonadism according to the AGE OF ONSET and to distinguish between:

(1) *Early hypergonadism*, in which the onset is prepubertal. This is subdivided into:

(a) True precocious puberty.

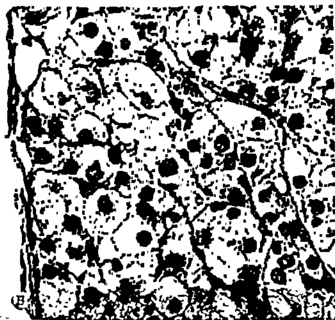
(b) Precocious pseudopuberty.

(2) *Late hypergonadism*, which develops after puberty and can be subdivided into:

(a) Constitutional hypergonadism.

(b) Hypertestoidism of the adult, due to Leydig cell proliferation.

It will be noted that true precocious puberty is characterized by the proportionate, precocious development of both the seminiferous tubules and the Leydig cells, while precocious pseudopuberty of testicular origin is due to an excessive, sometimes neoplastic



Leydig cell carcinoma. — Man, age 32 years, claimed that his left testis was always larger than the right. 9 years after left testis was removed for a palpable nodular tumor, generalized metastases appeared, the patient eliminated 110 MU of gonadotrophins, 113 MU of folliculoids and about 1 gm of 17-KS/day. He remained robust throughout and lost weight only just before death, 10 years after removal of the primary neoplasm — A. Classic Leydig-cell neoplasm, consisting of trabeculae between which large sinusoids are visible. — B. Same tumor under high magnification. Note large vacuolized lipid-containing Leydig cells of typical appearance

(After P. Masson, Rev. Canad. de Biol. 2: 163, 1943.)

proliferation of the testoid-producing Leydig cells.

In adults, we speak of constitutional hypergonadism if both sperm production and testoid hormone secretion are excessive This condition is on the borderline of the normal. Adult hypertestoidism of testicular origin (not to be confused with that due to adrenal-cortical tumors) is invariably caused by interstitial cell hyperplasia or neoplasia

PATHOLOGIC ANATOMY

In true PRECOCIOUS PUBERTY and CONSTITUTIONAL HYPERGONADISM, both the seminiferous elements and the Leydig cells are excessively developed, at least for the age of the patient.

There are no clear-cut clinical syndromes attributable to an ISOLATED PROLIFERATION OF THE SPERMATOGENIC EPITHELIUM other than the non-virilizing tumors of the seminiferous cells. (See p 674.)

HYPERTESTOIDISM of testicular origin, including precocious pseudopuberty in males, is caused by hyperplasia or neoplastic proliferation of the Leydig cells. The latter may be benign (adenomas) or malignant (carcinomas). The malignant Leydig cell tumors can proliferate both by mitotic and by amitotic division. In patients bearing Leydig cell tumors the normal Leydig cells are usually atrophic (compensatory atrophy). Leydig cell carcinomas can metastasize through lymphatics or blood vessels, sometimes the metastases are enormous, weighing several Kg

INCIDENCE

All types of male hypergonadism are extremely rare, with the exception of the so-called familial or constitutional hypergonadism The latter is especially common in certain families and in some of the Southern races, but it is doubtful whether it should be regarded as a definite disease entity, rather than merely a special anthropologic type

PATHOGENESIS

CONSTITUTIONAL HYPERGONADISM in the adult and many types of true PRECOCIOUS PUBERTY are apparently of genetic origin, since they tend to occur in certain families and are unaccompanied by any other pathologic change which could explain their development. It is well to remember, however, that other types of true precocious puberty, with simultaneous excessive development of both the Leydig cells and the seminiferous elements are found in association with tumors or inflammatory lesions in the hypothalamic and diencephalic regions, hydrocephalus due to distention of the third ventricle, or pineal tumors. It is claimed that in all these cases nervous or mechanical stimulation of the adjacent anterior hypophysis is of pathogenic importance and that an increased production of pituitary gonadotrophins is responsible for the testicular growth. It will be recalled that excessive testis development may also occur in the earliest stages of acromegaly and other syndromes due to primary tumors of the hypophysis. In these cases other signs of hypophyseal hyperactivity are also manifest and hence they will be described in conjunction with the pituitary diseases.

It is possible, though by no means proven, that certain nervous centers may directly stimulate gonadal development, that is, without the intermediary of the anterior-hypophysis.

PRECOCIOUS PSEUDOPUBERTY and ADULT HYPERTESTOIDISM of testicular origin are invariably due to an increased testoid hormone production by hyperplastic, or neoplastic Leydig cells The cause of the Leydig cell hyperplasia is not known, but it is interesting in this connection that prolonged treatment with folliculoids causes Leydig cell tumors in hereditarily predisposed strains of mice (See also pages 636 to 638) It is also noteworthy that

increased gonadotrophin and folliculoid elimination have been reported in men with Leydig cell tumors.

CLINICAL COURSE

In patients with PRECOCIOUS PUBERTY or CONSTITUTIONAL HYPERGONADISM, that is, a proportionate excessive development of both Leydig and seminiferous cells, the clinical syndrome is merely characterized by the excessive development of the testes and the accessory sex organs. Only if cerebral or hypophyseal lesions are of etiologic importance do other manifestations complicate the clinical course.

HYPERTESTOIDISM due to hyperplasia or neoplastic proliferation of the Leydig cells is often conducive to *metabolic disturbances* especially nitrogen retention, and increased urinary elimination of 17-KS, folliculoids and gonadotrophins.

The condition is mainly characterized by an excessive, and, in prepubertal children, precocious development of all *male sex characteristics*. In prepubertal children this may lead to excessive growth of the penis with the development of pubic and axillary hair, beard and mustache growth, precocious libido (with or without other manifestations of mental precocity) and a deepening of the voice due to precocious maturation of the larynx There is a great tendency towards the loss of scalp hair with excessive hirsutism in other regions of the body

At the same time there is often precocious and disproportionate *growth in length*, especially of the trunk, while the arms and legs are comparatively short, due to early ossification of the junction cartilages Thus, the skeletal lesions are almost the exact reverse of those seen in hypotestoidism, and are somewhat reminiscent of achondroplasia.

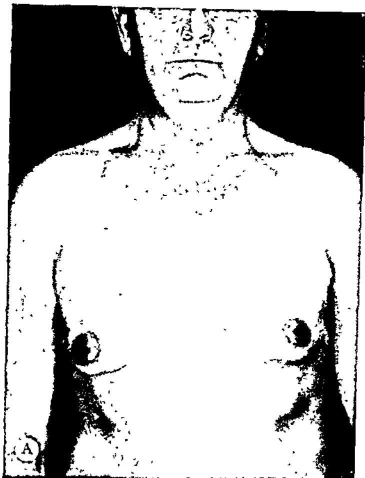
There is a great tendency towards nitrogen anabolism and increased *muscular development*, which often markedly augments muscular strength. In children this may lead to the "infant Hercules" type of appearance. It is noteworthy that even in seriously ill patients with generalized carcinomatosis due to metastases of Leydig cell tumors, muscular strength and vigor may be maintained until shortly before death and the patients exhibit an appearance of physical well-being quite disproportionate to their serious condition.

The *lymphocyte count* is frequently far below normal and the physiologic, pubertal *thymus involution* tends to be precocious.



Precocious pseudopuberty. 9½-year-old boy with Leydig cell tumor Note excessive genital and beard development with disproportionately short extremities. Musculature excessively strong

(After F Parkes Weber Guy's Hosp Rep 1929 — Sacchi's case)

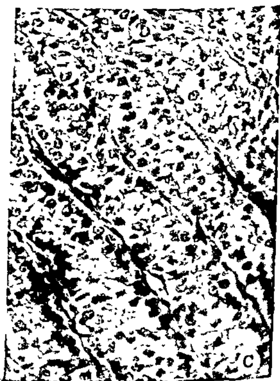


Lipid-cell tumor of the testis with gynecomastia. — A. Man, age 53 years, with "feminizing" testicular tumor. Note that this photograph, taken 9 months after operation, still shows marked gynecomastia. — B. *Macroscopic appearance of the* cut surface of the bright yellow *lipid-cell tumor, found* in the testis of the patient. — C. Histologic structure of the tumor. Note that most of the parenchyme consists of large, light sudanophilic lipid cells. It is questionable whether we should *consider the gynecomastia* as a sign of "feminization", since *testosterone (known to be produced* by the Leydig cells) also stimulates mammary growth.

Teilum now thinks these are Sertoli-cell tumors which produce folliculoids. They could be called "androblastomas", a term *which would include, arrhenoblastomas,* Leydig-cell tumors *and Sertoli-cell* tumors. The "folliculome lipidique" is a Sertoli-cell tumor with lipid storage.

(Courtesy of Dr. Gunnar Teilum.)





The secretion of the *sebaceous glands* is usually augmented and there is a tendency toward the development of *acne*.

In some patients with Leydig cell tumors, pronounced *gynecomastia* develops. This, as well as most of the above-mentioned manifestations of the disease, tend to disappear following ablation of the causative tumor but reappear in the event of carcinomatous recurrences.

DIAGNOSIS

The recognition of hypergonadism rarely presents any problems other than those concerned with the differential diagnosis of the various types.

True PRECOCIOUS PUBERTY and CONSTITUTIONAL HYPERGONADISM are recognised by the absence of any other specific lesion which could be of etiologic importance.

In PRECOCIOUS PSEUDOPUBERTY and ADULT HYPERTESTOIDISM of testicular origin the presence of a palpable testis tumor is of the greatest diagnostic significance. In doubtful instances a punch biopsy may help to identify the nature of this neoplasm. The presence in the urine of excessive amounts (in one case 1000 mg./day) of 17-KS, especially the metabolic end-products of testosterone (e.g., androsterone, etiocholanolone) and the absence of an increase in corticoid hormone metabolites (e.g., dehydro-iso-androsterone, 11-oxygenated steroids, active corticoids) are likewise characteristic of interstitial cell tumors.

PRECOCIOUS PUBERTY DUE TO LESIONS OF THE PINEAL REGION (p. 595), is mainly characterized by local signs of a brain tumor.

Unlike in CUSHING'S DISEASE and in ADRENAL-CORTICAL TUMORS, there are no local signs pointing to the presence of a hypophyseal or adrenal neoplasm and there is no tendency towards the development of hypertension, osteoporosis, diabetes or adiposity in primary hypertestoidism.

OSTEITIS FIBROSA DISSEMINATA WITH AREAS OF PIGMENTATION (fibrous dysplasia of the bones or Albright's disease) may also be associated with sexual precocity in boys, although this condition is exceedingly rare in the male. It is possible that in pertinent cases disturbances in the midbrain centers are responsible for the precocious development of the sex organs. The characteristic areas of cutaneous pigmentation and of focal bone absorption facilitate the differentiation of this condition from other types of hypergonadism. (See also pp. 583-586)

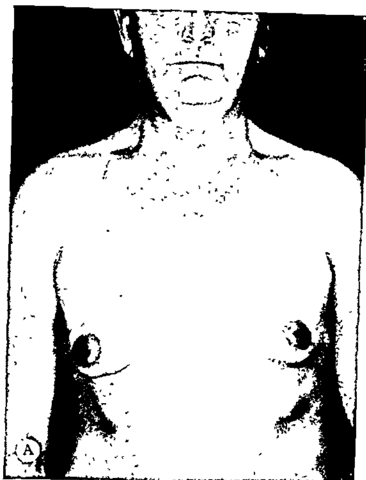
PROGNOSIS AND THERAPY

CONSTITUTIONAL HYPERGONADISM and true PRECOCIOUS PUBERTY require no therapy as they are not conducive to any serious disturbance. If the patient suffers from an excessive sexual drive, folliculoid hormone administration is frequently helpful, although care must be taken not to prolong treatment excessively, since otherwise severe testis atrophy and signs of feminization may ensue. Precocious puberty due to cerebral or pineal tumors should be treated surgically, whenever possible, but the prognosis is poor because of technical difficulties.

Patients with HYPERTESTOIDISM due to Leydig cell tumors, should always be treated surgically, unless extensive metastases render removal of the neoplastic tissue technically impossible. Only in this event is it advisable to apply X-ray or radium therapy, whose usefulness, if any, is always transitory.

HYPERGONADISM IN ANIMALS

TUMORS OF THE LEYDIG CELLS are comparatively common following prolonged treatment with folliculoids, in certain strains of hereditarily predisposed mice. It is noteworthy that under ordinary conditions folliculoids

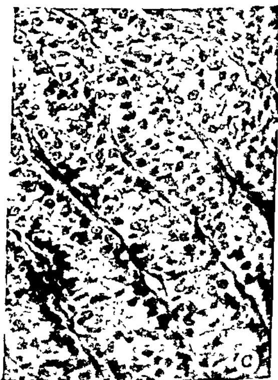


Lipid-cell tumor of the testis with gynecomastia. — A. Man, age 53 years, with "feminizing" testicular tumor. Note that this photograph, taken 9 months after operation, still shows marked gynecomastia. — B. Macroscopic appearance of the cut surface of the bright yellow lipid-cell tumor, found in the testis of the patient. — C. Histologic structure of the tumor. Note that most of the parenchyme consists of large, light sudanophilic lipid cells. It is questionable whether we should consider the gynecomastia as a sign of "feminization", since testosterone (known to be produced by the Leydig cells) also stimulates mammary growth.

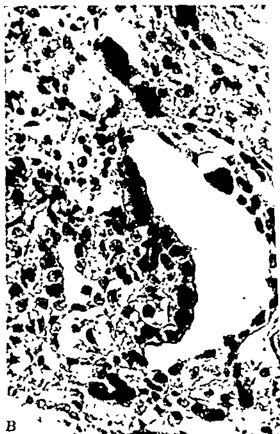
Teilum now thinks these are Sertoli-cell tumors which produce folliculoids. They could be called "androblastomas", a term which would include arrhenoblastomas, Leydig-cell tumors and Sertoli-cell tumors. The "folliculome lipidique" is a Sertoli-cell tumor with lipid storage.

(Courtesy of Dr. Gunnar Teilum.)






A


B




D

Teratoma of the testis ... ermatic vein by a neoplasm containing numerous ... of the blastocysts from the same neoplasm ... ng D Such formations have been confused with ... are probably embryonic centers, from which ... may commence — D. Normal blastocyst, shown for comparison

(Courtesy of Dr P Masson)

cause involution of the Leydig cells in all animals, including these predisposed strains. Perhaps the development of Leydig cell tumors represents an excessive compensatory reaction to the initial anti-Leydig cell effect of the folliculoids. Such experimental Leydig cell tumors may become malignant and produce extensive metastases. They can be transplanted to other animals and produce excessive amounts of testoids, as judged by the exaggerated accessory sex organ development in the tumor-bearing animals. (See also: pp. 636-638.)

In dogs, feminizing tumors of the testis are comparatively common. They are due to NEOPLASTIC GROWTH OF THE SERTOLI CELLS *and are characterized by an unusually high folliculoid hormone content (sometimes as much as twice the concentration found in mature ovarian follicles). On the basis of these observations it has been claimed that the production of folliculoids is a normal function of the Sertoli cells.*

TESTIS TUMORS IN GENERAL

The tumors of the gonads, which are essentially similar in either sex, have been described in some detail in the section · The Ovary; the endocrinologically most important Leydig cell tumors have been discussed in conjunction with male hypergonadism (see above) Hence cursory mention of the most important characteristics of the testicular neoplasms will suffice in this chapter.

It is now generally conceded that the great majority of the tumors of the testes are essentially teratoids, arising from multipotent sex cells. Even most of the unitissular forms appear to represent one-sided developments of originally tridermal teratomas. The adult seminiferous tubules, the interstitial cells, or the testicular stroma are but rarely the site of tumor formation.

EMBRYOMAS

The "adult" embryomas or teratomas of the testis exhibit a structure similar to that of the corresponding ovarian tumors They contain recognizable rudimentary organs, sometimes so arranged as to resemble a parasitic fetus Their growth is slow and many of them, even if present at birth, do not require surgical therapy until the patient reaches adulthood.

EMBRYOID OR MIXED TUMORS

These are tridermal growths, in which a variety of embryonic structures are intermixed, without any organoid arrangement. At the onset they may be benign and their structures of a comparatively mature type, but the majority tend to become malignant and then exhibit a great tendency toward the formation of multiple metastases.

"FALSE SEMINOMAS" (EMBRYONAL CARCINOMAS WITH LYMPHOID STROMA, DYSGERMINOMAS, GONIOMAS)

In addition to the above-mentioned synonyms, this tumor was also known under the name of "seminoma of Chevassu," or "round cell sarcoma of the testis." It usually contains necrotic and hemorrhagic foci and consists of polyhedral cells (vaguely resembling spermatogenic elements), the stroma being infiltrated with lymphocytes.

It becomes increasingly more probable, however, that these tumors are merely one-sidedly developed teratoids and could not be derived from the spermatoblasts. This conclusion is based upon the following facts . similar tissue occurs in otherwise typical mixed teratoid tumors, small teratoid foci are occasionally detected in otherwise uni-

acteristic of the false seminomas or "embryonal carcinomas." Their irregular parenchymatous cells, are smaller than those of the false seminomas. Unlike the latter, the true seminoma cells contain no glycogen and their stroma is not infiltrated by lymphocytes. Many of the tumor cell nuclei exhibit the filamentous structure (with a persistent spireme) so typical of primary spermatocytes.

The neoplasm exhibits a great tendency to invade the normal seminiferous tubules and tumor formation may arise simultaneously from several foci in the seminiferous tubules of a testis.

In agreement with their presumed tubular origin, no comparable neoplasms have ever been observed in the ovary.



Chorionepithelioma of the testis. Note typical chorionic villae [illegible]

[illegible]

The patient eliminated large amounts of LH
(Courtesy of Dr P Masson)

CHORIONEPITHELIOMAS

The chorionepithelioma (chorion carcinoma, chorioma) reproduces all *the characteristic morphologic and* clinical features of chorionepitheliomas *developing in other organs. Since these* have been described in detail in the sec*tion : "The Ovary," we shall not enu*merate them there. (See: p. 453.)

*Suffice it to state that testicular cho*rionepitheliomas are extremely malig*nant and conducive to increased gonad*otrophin production. This results in a *very high gonadotrophin content in the* urine (10,000 I.U., or more, per day) *and sometimes hormonal disturbances,* such as Leydig cell hyperplasia and *gynecomastia* with the secretion of colostrum.

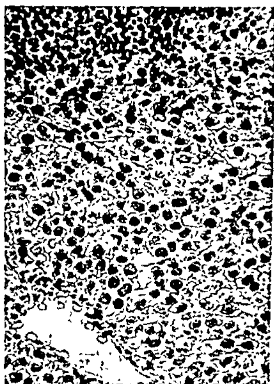
The treatment of choice is the surgical removal of the tumor, but this is rarely performed early enough to prevent fatal metastases and recurrences.

ADRENAL-CORTICAL TUMORS

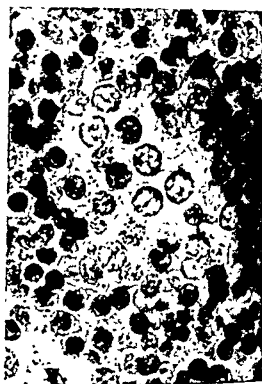
In rare cases, solid carcinomas of the testis may resemble the structure of *adrenal carcinomas. Since nodules of* ectopic adrenal-cortical tissue occa*sionally occur in the testis or its cap*sule, it has been assumed that adrenal*cortical neoplasms may primarily arise* in the male gonad. The number of confirmed pertinent cases is not sufficient to form a definite opinion concerning this point.

ADENOCARCINOMAS

Various types of solid or cystic *adenocarcinomas can develop in the tes*tis. These are probably also one-sided*ly developed teratoids. Their relation* to other teratoids is suggested by their *structure and by the fact that they are* conducive to greatly increased (10,000 I U., or more, per day) gonadotrophin elimination in the urine.



False seminoma (dysgerminoma) of the testis. The neoplasm consists of comparatively large clear cells, which contain glycogen and irregularly spherical nuclei. The stroma is infiltrated by lymphocytes.
(Courtesy of Dr P Masson.)



True seminoma (spermatocytic seminoma) of the testis. A group of large, clear cells, surrounded by smaller dark cells. There are numerous transitional forms between these two types. The large cells exhibit the typical filamentous structure of primary spermatocytes.
(Courtesy of Dr P Masson.)

form embryonal carcinomas (e.g., cartilage, squamous epithelial cells, intestinal epithelium), similar tumors also occur in the female gonad, the rapid growth of these extremely malignant neoplasms could yield favorable conditions for the "crowding-out" of other elements in originally mixed tumors, and finally, a few tumors manifestly derived from adult spermatoblasts (see · True Seminomas, below) exhibit an entirely different histologic structure.

Like other teratoid neoplasms, the false seminomas are conducive to the excess excretion of gonadotrophins, although usually in much smaller amounts than are found in the urine of patients with chorionepitheliomas of the testis.

TRUE SEMINOMAS

It is well to identify this neoplasm by the term "true seminoma," since most early publications concerning "testicular seminomas" actually dealt with the embryonic carcinomas mentioned above, which were hitherto misinterpreted as seminomas.

Masson suggests the name "gonioma" for the false seminomas, since they may be derived from the first proliferation of the gonocytogenic cell; he designates the true seminomas, derived from the second proliferation, as "spermatocytic seminoma" (séminome spermatocitaire).

The extraordinarily rare true seminomas are greyish-white, edematous tumors. They do not contain necrotic and hemorrhagic foci, such as are char-

Monograph (68 pages, 96 references, no illustrations) on the symptomatology, pathogenesis, diagnosis and treatment of the male climacteric (In French)

MASSON, P.: *Deux Cancers Leydigiens de l'Homme. Leur Comparaison avec les Tumeurs Interstitielles Expérimentales de la Souris.* Rev. canad de Biol. 2, 168 (1943)

An excellent review (73 pages, 24 references, numerous excellent illustrations) on the pathogenesis of interstitial cell tumors of the testis, with a detailed description of two personally examined cases (In French)

MASSON, P.: *Etude sur le Séminome.* Rev. canad. de Biol 5, 361 (1946).

Very authoritative review (26 pages, 7 references, numerous excellent illustrations) concerning the relationship of the "true" and "false seminomas" of the testis. (In French)

DE MELLO, R. F.: *Os Hormonios Testiculares* Sao Paulo Ltda imprimiu (1936).

Monograph (83 pages, 9 illustrations, 15 references) surveying the physiology of the testis, mainly from the experimental point of view. (In Portugese)

MIOTTI, TITO: *Lo Sperma Biologia Patologia Clinica* Att Sc Med 20, 7 (1942)

Monograph (178 pages, 63 illustrations and more than 600 references) concerning the biology and pathology of sperma and its application to the treatment of sterility in animals and man. A very systematic study of the subject by an author who has done a great deal of original work in this field (In Italian)

OBERNDORFER, S.: *Die inneren männlichen Geschlechtsorgane.* F. Henke und O Lubarsch's Handbuch der speziellen pathologischen Anatomie und Histologie, 6 Harnorgane männliche Geschlechtsorgane 427 (1931)

Very exhaustive treatise (464 pages, numerous illustrations and a practically complete survey of the pertinent literature) in which the entire pathologic anatomy of the testis is discussed mainly from the purely morphologic view-point This undoubtedly represents one of the best and most complete sources of pertinent literature now available (In German)

PALAZZOLI, M *Déficiences sexuelles masculines d'origine emotive* Masson et Cie, Publ, Paris (1946)

A small booklet (146 pages, no illustrations or references) which attempts to give an elementary summary of sexual deficiencies due to emotional causes in men It is illustrated by many case reports (In French)

PULLEN, R L, J. A WILSON, E C HAMBLEN AND W K CUYLER *Testicular Dysfunction Clinical Reviews in Andrologic Endocrinology. I. Physiology, Functional Pathology and Diagnosis. II. Treatment of Androgenic Failure III. Treatment of Seminal Failure.* J. Clin Endocrinol. 2, 577, 655, 730 (1942)

A critical review (24 pages, 389 references, no illustrations) of the pathogenesis and therapy of the various types of male hypogonadism

SIMONNET, H AND M. ROBEY *Les androgènes Etude biologique, clinique et thérapeutique.* Masson et Cie, Publ, Paris (1941).

A monograph (267 pages, 15 figures, 1827 references) concerning testoid hormones, which can act as a guide to the most important publications in the old literature, now somewhat out of date (In French)

TANDLER, J UND S GROSZ *Ueber den Einfluss der Kastration auf den Organismus. I Beschreibung eines Eunuchenskelets. II Die Skopzen III Die Eunuchoide.* Arch. fur Entwicklungsmechanik der Organismen 27, 35 (1909), 29, 290 and 30, 236 (1910).

A description of the habits and anatomic characteristics of the Skopts, a religious sect practicing early castration in boys (In German)

THOREK M: *The human testis* J. B Lippincott Co, Publ, Philadelphia (1924).

A monograph (548 pages, 308 illustrations, numerous references) concerning the morphology, physiology and pathology of the testis in men Many valuable clinical observations, but the discussions are now outdated

VORONOFF, S AND G ALEXANDRESCU *Testicular Grafting from ape to man* Translated by T C. Merrill Brentano's Ltd Publ, London, England (1929)

A monograph (125 pages, 39 figures, no illustrations) concerning the author's results with testicular transplants from ape to man

VORONOFF S AND G ALEXANDRESCU: *La greffe testiculaire du singe à l'homme.* Gaston Doin & Cie, Publ Paris (1930)

A monograph (88 pages, 39 illustrations no references) which essentially, represents a French version of the work discussed above (In French)

WAGENSEIL, F *Chinesische Eunuchen (Zugleich ein Beitrag zur Kenntnis der Kastrationsfolgen und der rassialen und körperbaulichen Bedeutung der anthropologischen Merkmale)*

A most interesting monograph (53 pages, 6 tables, few references) concerning the author's observations on 31 Chinese eunuchs who had been castrated (partly before, partly after, puberty) in agreement with social custom under the last Chinese Imperial dynasty (In German)

ADENOMAS

Only very few cases of true testicular adenomas have been described. They occasionally occur in cryptorchid or atrophic testes in the form of small yellowish nodules, a few mm. in diameter.

Histologically, they consist of regular tubules, lined by poorly developed spermatogenic cells. There are various transitional types, intermediate in structure between the least differentiated seminiferous tubules of the adenoma and the fully differentiated tubules of the normal testicular parenchyme.

OTHER TESTICULAR TUMORS

Among other neoplasms, which may occur in the testis, only the LYMPHOSARCOMA, MYOMA, CHONDROMA, FIBROMA, and SPINDLE-CELL SARCOMA deserve cursory mention. They are very rare and show no tendency to produce any endocrinologically important changes.

REFERENCES

BENOIT, J *Recherches anatomiques, cytologiques et histophysiologiques sur les voies excrétrices du testicule chez les mammifères. Contribution à l'étude de quelques problèmes de cytologie générale relatifs à la cellule glandulaire.* Imprimerie Alsacienne, Strasbourg (1925).

An excellent monograph (232 pages, 100 excellent illustrations, numerous references) concerning the various subjects outlined in the title. (In French.)

DORFMAN, R I *Biochemistry of Androgens.* In The Hormones Pincus, G. and K V. Thimann (Ed). Academic Press Inc, Publ, New York (1948)

An excellent brief synopsis (81 pages, many figures and tables, 225 references) of recent advances concerning the physiology and pathology of testoid metabolism.

FRIEDGOOD, H B. *Concerning the biochemistry and the physiological and clinical significance of the sex hormones and 17-keto-steroids* In The Chemistry and Physiology of Hormones p. 195, F R Moulton, Ed, American Association for the Advancement of Science, Publ. (1944.)

A brief review (48 pages, numerous tables, few references) concerning the metabolism of 17-KS and testoids

GALLAGHER, T F *The excretion of steroid hormones in urine.* In The Chemistry and Physiology of Hormones p 186, F R Moulton, Ed., American Association for the Advancement of Science, Publ (1944)

A brief review (9 pages, few figures, charts and references) concerning the urinary excretion of 17-KS and other steroids.

HIGIER, S. *Les fonctions sexuelles mâles et leurs troubles.* G Doin & Cie, Publ, Paris (1932).

A treatise (391 pages, 4 figures, 355 references) mainly concerned with the emotional and nervous mechanism of copulation under normal and pathologic conditions (In French.)

HOTCHKISS, R S.: *Fertility in Men. A Clinical Study of the Causes, Diagnosis and Treatment of Impaired Fertility in Men.* J. B Lippincott Company, Publ, Philadelphia (1944).

Monograph (216 pages, 95 illustrations, numerous references) concerned with the pathogenesis and therapy of impaired fertility in men, written mainly from the practical standpoint. Excellent descriptions of pertinent technics, such as those concerned with morphologic studies of sperm, punch biopsies of the testis, vasoepididymal anastomosis, etc

LAGERLOF, N.: *Morphologische Untersuchungen über Veranderungen im Spermabild und in den hoden bei bullen mit Verminderter oder Aufgehobener Fertilität* Acta Path et Microbiol. Scandinav, Supplementum *XIX*, 8 (1934).

Monograph (254 pages, 51 excellent illustrations, 273 references) concerning morphologic changes in the testis and the sperma of bulls with decreased or abolished fertility This is a very useful summary of the practical applications of sterility research to animal breeding (In German.)

LUCIEN, M, J. PARISOT AND G. RICHARD. *Traité d endocrinologie Le testicule.* G. Doin & Cie, Publ, Paris (1942)

This volume (352 pages, 46 illustrations, few references) forms part of a treatise on endocrinology Theoretic and practical problems are approximately equally stressed (In French)

MARTEL, A *Le Climactere Masculin* Laval Médical Inc, Quebec (1946)

Experimental Physiology. — *Rowntree et al.* (1935) claimed that certain thymus extracts cause marked acceleration in SOMATIC GROWTH and precocious sexual development in the rat, and that these effects became increasingly more evident in subsequent generations of similarly treated animals. Earlier growth-stimulation by thymus preparations even led to the assumption that there is a special growth-promoting thymus hormone "thymocrescin" (*Asher*, 1930). On re-examination, these data failed to be confirmed. If occasional thymus extracts do cause some acceleration of growth under certain experimental conditions, this could be due to such non-hormonal constituents as glutathione, cystine, ascorbic acid, etc.

The more recent claim (*Bomskov*, 1942) that the thymus contains CARBOHYDRATE METABOLISM influencing steroids, likewise lacks confirmation. The same is true of many other effects attributed to thymectomy and thymus extract injections, such as changes in BONE structure, the CARDIOVASCULAR apparatus, the BLOOD PICTURE, egg SHELL FORMATION in birds, etc.

In the old literature, much emphasis was placed upon the inhibition of METAMORPHOSIS (*Gudernatsch*, 1914) and the deficient bone development (*Stettner*, 1916) in tadpoles fed with thymus. Since many other unbalanced diets cause similar disturbances, these changes cannot be attributed to any special thymus hormone.

The best established experimental observations concerning the thymus have been brought out during the last ten years by work concerned with the influence upon this organ of NON-SPECIFIC DAMAGE and STEROID HORMONES. It appears that folliculoids and to a lesser extent, even other steroid hormones, cause rapid thymus involution, not only in intact, but also in adrenalectomized animals. Non-specific damaging agents of all kinds have a similar effect only if the adrenals are intact. It has been assumed therefore, that various types of stress cause the thymus to involute through the intermediary of the adrenals. In adrenal-cortical hypoplasia and following adrenalectomy, when this involution is impeded, resistance to non-specific damage is concurrently decreased. The significance of this thymic response during resistance to non-specific stress is still unknown.

NORMAL MORPHOLOGY

ANATOMY

The fully developed human thymus consists of two lateral lobes, placed in close contact along the mid-line. It is situated within the thorax but reaches up to the neck, extending from the 4th costal cartilage, craniad sometimes as high as the lower border of the thyroid. Anteriorly, it is covered by the sternum and the origins of the sternohyoid and sternothyroid muscles. Dorsally, it is attached to the pericardium and separated from the aortic arch and the large vessels by a fascia. Its cranial end lies in front of the trachea, behind the sternohyoid and sternothyroid muscles. The two lobes, which are not necessarily of equal size, may be united by a distinct isthmus. Sometimes, there is an intermediate-lobe between the two main parts.

The color of the thymus is pinkish-gray, its surface lobulated and its consistency soft. It measures about 5 cm. in length, 6 mm. in thickness and 4 cm. in breadth at its base where it is broadest. The organ weighs about 15 gm. at birth and 35 gm at puberty, but subsequently involutes, reaching 25 gm. in a young adult of about 25 years and gradually diminishing to about 6 gm at 70 years of age.

IX

THE THYMUS

HISTORIC INTRODUCTION

The term "thymus" is derived from the Greek word THYMOS which means both COURAGE and THYME. *Galen* suspected that the thymus is the "center of courage and affection," because of its close relationship to the heart; the actual shape of the organ resembles the leaves of the thyme plant.

Galen and *Rufus of Ephesus*, were probably the first to describe the thymus in a superficial manner, but an accurate anatomic description, illustrated by pictures, was only given in 1650 by *Vesalius*. In 1671, *Regner de Graaf* (whose name is well-known through his discovery of the Graafian follicles in the ovary) described "central cavities" in the thymus, but these were subsequently shown to be artefacts due to autolysis. In 1736, *Ruyach* believed he had found a central excretory canal of the thymus. This was probably a large vein, since the existence of an excretory canal was denied even by his contemporaries, *Cowper* and *Haller*, who recognized the thymus as a lymphoid organ. It is of historic interest that it took about 200 years to correct these anatomic misconceptions completely, although as early as 1812, *Lucae* began to doubt the existence of central cavities and to suspect that the organ consisted of two distinct portions, a cortex and a medulla

In 1846, the English physician *Arthur Hill Hassall* described the epithelial corpuscles which now bear his name Probably the most fundamental study of the thymus is that of the Swedish morphologist *J. A Hammar*, who spent about 35 years on an investigation of the histology and histopathology of this organ.

Diseases. — In 1614, *Felix Platter* published the first report of a so-called "thymic death" in an infant who died by suffocation, presumably because of great thymic enlargement. Later, in Germany, *Arnold Paltauf* (1889) described a form of dwarfism with "STATUS THYMICO-LYMPHATICUS." Its prominent features were enlargement of the thymus and other lymphatic organs (lymph nodes, bone marrow, spleen), with hypoplasia of the adrenals and of the cardiovascular apparatus. Patients with this syndrome appeared to be subject to sudden death upon exposure to comparatively mild types of stress; this drew attention to the possible relationship between the thymus and general resistance.

Wiegert (1901) was the first to notice an association between MYASTHENIA GRAVIS and abnormalities of the thymus. Subsequent investigators have shown that hyperplasia and tumors of the thymus occur more frequently in myasthenia gravis than could be explained on the basis of mere coincidence. Irradiation often proved beneficial, and *Clagett* and *Root* (1944), at the Mayo Clinic, repeatedly obtained improvement or complete remission in myasthenia gravis by removal of the thymus. In view of the frequent association of thymus hyperplasia and profound muscular weakness in Graves' and Addison's diseases, the above observations deserve to be carefully followed, since they offer some hope of clarifying the, so far mysterious, function of this organ

Experimental Physiology. — *Rowntree et al.* (1935) claimed that certain thymus extracts cause marked acceleration in SOMATIC GROWTH and precocious sexual development in the rat, and that these effects became increasingly more evident in subsequent generations of similarly treated animals. Earlier growth-stimulation by thymus preparations even led to the assumption that there is a special growth-promoting thymus hormone "thymocrescin" (*Asher*, 1930). On re-examination these data failed to be confirmed. If occasional thymus extracts do cause some acceleration of growth under certain experimental conditions, this could be due to such non-hormonal constituents as glutathione, cystine, ascorbic acid, etc.

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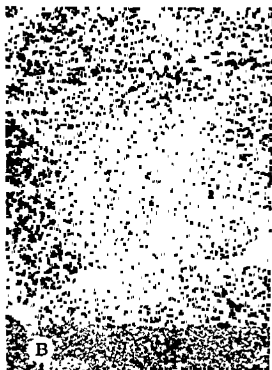
Since any intercurrent disease is *likely to influence the weight of the thymus*, all these figures are subject to great variations.

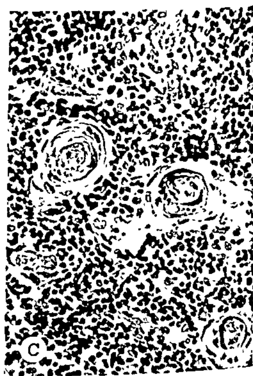
HISTOLOGY

The histologic structure of the thymus is also subject to great variations, depending upon the age and general condition of the individual. In the fully developed gland, a cortex and a medulla may be distinguished.

The CORTEX consists of a densely packed mass of small lymphocyte-like cells, which are usually referred to as thymocytes. These have an average diameter of 6 μ and only a trace of cytoplasm around their darkly staining nuclei. Histologically, they can hardly be distinguished from ordinary lymphocytes and therefore some histologists doubt the justification of a special







Immature thymu
child Note the
light medulla, in
by fat — B. A
lobule from adjacent ...
visible in the center of the medulla (Low magnification) — C. Three typical ...
(High magnification) (Courtesy of Dr W Bonin)

designation for these cells. Between the thymocytes are elongated reticular cells, with several long processes and very indistinct cell outlines. These cells contain round or oval nuclei, which are comparatively poor in chromatin.

The MEDULLA consists almost exclusively of reticular cells, between which there are only a few thymocytes. *Irregularly scattered throughout the* medulla, there are also about one million rounded, eosinophilic structures "Hassall's concentric corpuscles." These vary in diameter between 30 and 100 μ and are composed of "onion-bulb-like," concentrically arranged, flat, squamous, epithelial cells, the central ones showing degeneration and hyalinization with gradual transformation into colloid debris.

Eosinophilic myelocytes and plasma cells may also occur in the medulla but lymphatic nodules, *with germinal centers*, are most exceptional anywhere in the thymus.

The STROMA consists of entodermal reticular cells, and of mesenchymal connective tissue and perivascular reticular cells (see: "Embryology").

Due to the heavy lymphocytic infiltration, the *epithelial nature of the reticulum* is not evident in the normal thymus. However, if most lymphocytes are destroyed as in the "alarm reaction" or after X-ray treatment, the epithelial nature of the reticulum becomes obvious again Unlike other reticular cells, those of the thymus usually do not store intravenously-*injected particulate matter*, although in the alarm reaction they phagocytose the debris of degenerating thymocytes, and in certain diseases (lipid histiocytoses) they are laden with lipid droplets.

The ARTERIES of the thymus come from the internal mammary and superior and inferior thyroid arteries. The veins end in the left innominate and thyroid veins.

The LYMPHATICS of the thymus course to the anterior mediastinal, tracheobronchial and sternal lymph nodes.

There are only very fine NERVE filaments in the thymus. These are derived from the sympathetic and vagus. Branches from the descendant hypoglossus and phrenic nerves reach the capsule but fail to penetrate into the thymus.

COMPARATIVE MORPHOLOGY

The thymus is present in all vertebrates *although its shape, size and* position are extremely variable. In certain lower vertebrates (e g., birds) it extends along the neck in the form of irregular separate nodules and in addition, there is, in the coccygeal region, a thymus-like organ, the "bursa Fabricii."

EMBRYOLOGY

In man, the initially hollow thymic *primordia develop from the third pair* of pharyngeal pouches, towards the end of the sixth week of embryonic life Subsequently, they become solid and their upper ends tend to atrophy. The enlarged lower ends unite superficially during the 8th week and descend into their permanent position within the *thorax Towards the 10th week, the* originally purely epithelial structure is gradually transformed into a reticulum whose interspaces are invaded by small thymocytes The lymphatic invasion proceeds throughout embryonic life and during the 3rd month, there is definite differentiation into a separate cortex *and medulla. Hassall's corpuscles are* apparently derived from the reticular cells.

The normally involuting, cranial ends of the thymic primordia may persist, thus forming cervical prolongations or separate accessory cervical thymi.

THEORIES CONCERNING THE HISTOPHYSIOLOGY OF THE THYMUS

Since it is still not proven that the thymus is an endocrine gland, it would

Since any intercurrent disease is likely to influence the weight of the thymus, all these figures are subject to great variations.

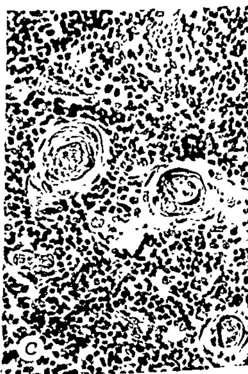
HISTOLOGY

The histologic structure of the thymus is also subject to great variations, depending upon the age and general condition of the individual. In the fully developed gland, a cortex and a medulla may be distinguished.

The CORTEX consists of a densely packed mass of small lymphocyte-like cells, which are usually referred to as thymocytes. These have an average diameter of 6 μ and only a trace of cytoplasm around their darkly staining nuclei. Histologically, they can hardly be distinguished from ordinary lymphocytes and therefore some histologists doubt the justification of a special







Immat
child
light m
by fat
lobule
visible in the center of the medulla (Low magnification) — C. Three typical
(High magnification) (Courtesy of Dr W Bonin)

can be removed completely in one piece, even from very young rats, with no operative mortality.

EFFECTS OF THYMECTOMY AND THYMUS EXTRACT INJECTIONS

It is evident from the Historic Introduction that neither complete thymectomy nor the injection of thymus extracts produce any detectable derangement in experimental animals or man. Hence, by classic criteria, there is no evidence for the existence of a thymus hormone. However, the consistent response of this organ to endocrine stimuli (see: "Stimuli Influencing Thymus Structure") suggests that it is of importance under certain conditions of stress, although we have not yet succeeded in devising experimental conditions to prove such a function.

STIMULI INFLUENCING THYMUS STRUCTURE

Extirpation of Endocrine Glands — ADRENALECTOMY has been claimed to produce a hyperplasia of the thymus, but this is not entirely correct. Removal of the adrenals merely prevents the various types of thymic involution and causes the organ to assume and maintain its maximal prepubertal size.

This prevention of thymus involution by adrenalectomy is due to a deficiency in corticoids rather than adrenaline: *adrenaline* fails to affect the thymus of adrenalectomized animals, but *corticoids* induce a full involution.

Various *other steroids* are likewise capable of causing thymus involution in adrenalectomized animals in the following order of decreasing activity folliculoids, testoids, luteoids and corticoids. The antithymic effect appears to be proportionate to the folliculoid activity of the various steroids and is apparently not influenced by any of the other independent pharmacologic actions (See: "The Steroids.")

It is noteworthy that apart from steroid hormones few *drugs* or damaging agents can influence the thymus of the adrenalectomized animal. Exceptions: direct exposure of the thymus region to ionizing radiations, pyridoxine-deficient diets, treatment with mustards, trypoflavine, Na-cacodylate

Adrenalectomy combined with *castration* (of males or females), produces an even more rapid development of the thymus than adrenalectomy alone, presumably because not only the adrenal but also the gonadal hormones are lacking.

HYPOPHYSECTOMY has been claimed to cause rapid and pronounced thymus involution, especially in the rat, but reexamination shows that this is not entirely correct The adrenals of the hypophysectomized animal are not immediately inactivated by removal of the anterior-lobe and presumably, the shock of the operation itself elicits a discharge of corticoids which in turn cause thymus involution If hypophysectomized animals are maintained in good condition for some time after the operation, their thymus remains fairly well developed and is almost as resistant to "accidental involution" as is that of the adrenalectomized animal.

Various steroid hormones, which cause thymus involution and somatotrophin, which stimulates thymic growth, remain effective after hypophysectomy.

GONADECTOMY in either sex partly protects the thymus against physiologic involution due to aging, and thus increases thymic size above the normal for the corresponding age, especially in postpubertal animals. This is due to deficiency in the gonadal hormones.

Gonadectomy does not change the normal effect of steroid hormones or of alarming stimuli upon the thymus.

PARTIAL THYMECTOMY induces only slight compensatory hypertrophy of the remnant.

be futile to discuss the many theories concerned with the cellular processes involved in the production of theoretic "thymus hormones" or the pathways of their secretion, etc. There is fairly good evidence indicating however, that substances liberated from the bodies of decomposing thymocytes, perform important physiologic rôles, even if they are not hormones in the original sense of this word

Under various conditions of stress, and under the influence of certain steroid hormones, the thymocytes disintegrate and their bodies are taken up by macrophages in the thymic reticulum. These macrophages subsequently migrate into the regional lymph nodes and hence, through the lymphatic vessels, bring thymocyte material into the blood. The substances thus liberated from the thymus have been claimed to play a rôle in immunologic reactions and regenerative processes, but the exact nature of their function is still unknown.

CHEMISTRY OF THE THYMUS

Thymus tissue contains about 85% water and 15% solids. Of the latter, nucleoproteins and nucleohistones are the most important, although the thymus also contains some lipids, glycogen, vitamins and traces of inorganic material. The comparatively large amount of phosphorus in the thymus is in organic combination, chiefly in nucleates.

EXPERIMENTAL PHYSIOLOGY OF THE THYMUS

EXPLANTATION AND TRANSPLANTATION OF THE THYMUS

Following EXPLANTATION, thymus tissue continues to grow in a rather typical manner in vitro and the thymocytes behave in every respect like lymphocytes Thus, they may change into plasma cells or phagocytosing polyblasts. The true epithelial nature of the thymic reticulum becomes particularly obvious in explants TRANSPLANTATION of the thymus is readily feasible in most experimental animals.

TECHNIC OF THYMECTOMY

In MAN, thymectomy is usually performed through a transverse section, just above the manubrium sterni After separating the fascia and muscle layers, the exposed thymus is clamped between two hemostats and gradually pulled upwards, great care being taken to clamp every small blood vessel. When sufficiently isolated, the base of the thymus is carefully ligated and the tissue excised. Following this, the muscle and skin wounds may be closed and the operation concluded without drainage.

Thymectomy is also possible in most experimental animals. In the RAT, which is frequently used for this type of study, the intervention is approximately the same as in man, except that the great size and comparatively deep location of the thymus necessitate a longitudinal incision through the sternum, splitting the latter about half its length. Both pleural cavities are usually opened, but since the actual extirpation does not take more than a fraction of a minute, respiration is not seriously impeded. To facilitate rapid closure of the wound, one or two stitches are loosely laid through the intercostal spaces, laterad from the thymus before opening the pleural cavities. After extirpation of the gland, pulling these threads closes the gap immediately, gentle pressure upon the thorax expresses the air from the pleural cavities and thus assures re-expansion of the lungs. With this technic, the organ

are detectable, but the involution at puberty is always striking, as stated above. Presumably the increased folliculoid-hormone production during gestation and the great stress upon metabolism occasioned by both pregnancy and lactation are responsible for the further involution of the thymus during these conditions.

Other Conditions. — Other conditions, such as exposure to nervous or even purely mental stress, forced muscular exercise, anoxia, extremes of temperature, trauma, hemorrhage or intoxication with various drugs, all produce *thymus atrophy*, as part of the general-adaptation-syndrome which they elicit. *Curiously, calcium administration* appears to inhibit thymus involution during the alarm reaction.

X-RAYS take a special position. Irradiation of the body, while the thymus is protected by a shield, causes thymus atrophy only in the presence of the adrenals, but direct irradiation of the thymus causes it to involute, even after adrenalectomy. Apparently, radiation sickness acts as an alarming stimulus *through the adrenals, just as other* noxious agents, while direct exposure of thymus tissue to X-rays causes *involution due to a local effect.*

DISEASES OF THE THYMUS

APLASIA and HYPOPLASIA of the thymus are comparatively rare and have been claimed to occur most frequently in hypoplastic and mentally deficient individuals. These conditions must be clearly differentiated from the "accidental thymus involution" following acute *exposure to non-specific damaging* agents (see. "General-Adaptation-Syndrome").

HYPERPLASIA of the thymus is characteristic of the so-called status thymico-lymphaticus. The latter has been discussed in the chapter on the Adrenals, since it is usually accompanied by *hypoplasia of the adrenal cortex.* The unusually marked development of the thymus in other types of adrenal insufficiency (clinical or experimental), and in hyperthyroidism, has also been mentioned in the corresponding sections of this book It is doubtful, however, whether a true status thymico-lymphaticus exists, since the thymus weights, recorded in allegedly pertinent cases, are within the normal range. As stated elsewhere, in average autopsy material the thymus weight is *far below normal* owing to the thymus involution accompanying the general-adaptation-syndrome elicited by *most fatal diseases.* Investigations during the First World War clearly indicate that in healthy young adults, suddenly killed in action, the thymus is as large as it was supposed to be in status thymico-lymphaticus. Nevertheless, it is noteworthy that in hypoplastic individuals with an undeveloped adrenal cortex, there tends *to be an enlargement of the thymus and* of the lymphatic organs, accompanied by hypoplasia of the cardiovascular *system and a great predisposition to* sudden death upon exposure to a variety of non-specific damaging agents.

The constitutional hyperthymic syndrome (*Pende*) of children is presum*ably a related condition. It is charac*terized by enlargement of the thymus, hypoplasia of the adrenals, "exudative diathesis" and marked hypogenitalism.

EDEMA, often accompanied by small HEMORRHAGES in the thymus, is likewise frequently seen in patients who die from acute infectious diseases or other conditions conducive to sudden non-specific damage.

INFLAMMATIONS, sometimes accompanied by abscess formation, can occur *in the thymus in the course of generalized* septicemia.

The most important primary diseases *of the thymus are its* TUMORS. For these, the word "thymoma" has been

Extirpation of OTHER ENDOCRINES does not significantly influence thymus structure except through the non-specific damage of the surgical interventions.

Hormones. — STEROID HORMONES cause thymic involution in proportion to their folliculoid potency in intact, adrenalectomized, or gonadectomized animals (see· p. 683).

THYROID HORMONE overdosage may cause some enlargement of the thymus, but only under optimal conditions of dosage and diet. The mechanism of this effect has not yet been determined.

HYPOPHYSEAL EXTRACTS with "thymotrophic" (thymus enlarging) activity have been described. Purified somatotrophin is especially active in this respect, but thyrotrophin may also play a part.

Purified gonadotrophic and adrenotrophic preparations cause thymic involution in proportion to the steroid-hormone production which they elicit in the gonads and adrenals respectively.

None of the OTHER HORMONES have been shown to exert any influence upon the thymus, not accountable to non-specific damage

Diseases. — In STATUS THYMICO-LYMPHATICUS, the characteristic adreno-cortical hypoplasia is accompanied by an over-development of the thymico-lymphatic apparatus. Some thymus enlargement is also frequently seen in other types of adreno-cortical insufficiency, such as ADDISON S DISEASE

In various types of HYPERTHYROIDISM, the thymus is usually excessively developed, if the cachexia has not progressed very far Infiltrations may occur in the thymus in various types of LYMPHATIC LEUKEMIA Thymus hyperplasia or even thymic tumors are sometimes associated with MYASTHENIA GRAVIS. (See. pp 685-688)

OTHER DISEASES usually cause thymus atrophy in proportion to the non-specific damage which they elicit This so-called "accidental thymus involution" is particularly manifest in very acute and severe infections or intoxications, especially in children in whom the thymus is normally large.

Diet. — Most qualitatively or quantitatively insufficient diets cause thymus involution in proportion to their general damaging effect.

Very little is known about diets having a specific influence upon thymic development. *Choline deficiency* produces thymic hemorrhages and involution, which are allegedly too severe to be merely ascribed to the accompanying systemic damage. *Fasting* tends to cause a much greater and more rapid decrease in the weight of the thymus than in that of other organs.

Age. — The thymus of most animal species, including man, is well developed at birth and continues to grow until approximately the time of puberty. After this, it undergoes a comparatively rapid involution until, in the senile individual, practically no lymphatic tissue is left. At this time the lymphatic elements are replaced by fat tissue, but the Hassall's corpuscles persist.

Sex. — In most animal species, the thymus is larger in the male than in the female, presumably because the female sex hormones have a greater anti-thymus effect than the testoids.

Season, Hibernation. — Seasonal variations in thymus size are particularly obvious in hibernating animals In these, and also in amphibia, the entire organ involutes during the dormant stage, due to disappearance of thymocytes, while the reticulum tends to proliferate. Probably the lymphatic tissue of the thymus acts as a reservoir, which supplies nutritive materials during the hibernating season. Its involution during hibernation is noteworthy, since the gonads and adrenals, the main sources of anti-thymic hormones, are also atrophic at this time.

Estrus, Puberty, Pregnancy and Lactation. — During the sexual cycle, only minor variations in thymus size

used more or less loosely, irrespective of their histologic structure. *Dermoids* are comparatively frequent in the thymus and its surroundings, but they have no endocrinologic interest. The organ may also be the site of *lipoma, myxoma,* and *fibroma* formation. These likewise cause no characteristic manifestations other than those due to pressure by the neoplastic tissue. Thymus "*adenomas*" are extremely rare. They consist almost exclusively of reticular cells and Hassall bodies. Thymic *cysts* are likewise exceptional. They are lined by a ciliated or squamous epithelium



Thymoma. Hepatic metastasis of a thymoma in a 59-year-old man, without myasthenia gravis (Courtesy of Dr P Masson)

Among the malignant thymomas, carcinomas of the epithelial reticulum and *spindle cell sarcomas* of the ordinary connective tissue are noteworthy The most characteristic malignant tumor of the thymus is a round-cell tumor, often designated as a *lymphosarcoma*

CLINICAL MANIFESTATIONS

The commonest and most important manifestations of thymus tumors are those due to LOCAL PRESSURE Dyspnea and cyanosis are often referred to as "thymic asthma" or "thymic stridor." They are probably due to direct pressure of the enlarged thymus upon the trachea and the nerves in its vicinity. Coughing, dysphagia, a very unpleasant sensation of pressure behind the sternum, and irregularities in the cardiac beat may also result. Pressure upon the recurrent nerves can cause vocal disturbances, sometimes culminating in total aphonia. Often compression of the blood vessels around the thymus leads to swelling of the neck and the development of a marked collateral circulation over the upper anterior thorax and the neck, as well as cerebral congestion accompanied by headaches, vertigo, and epistaxis.

Certain primary carcinomas of the thymus are occasionally associated with



Thymoma. Small thymoma in a man who suffered from myasthenia gravis The tumor is here seen to invade a large blood vessel and consists mainly of epithelioid reticular cells, reminiscent of Hassal's bodies (Courtesy of Dr P Masson)









Thymoma. — A. P[illegible] tumor on arch of aorta (very low magnification) — B. Higher [illegible] and magnification of [illegible] (center) cystic ca[illegible] reminiscent of Ha[illegible] metastases (very [illegible] showing liver tissu[illegible]

[illegible] (Courtesy of Dr. [illegible])

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A monograph (172 pages, 820 references) concerning the "status thymico-lymphaticus" and its relation to various other endocrine diseases. (In German)

JOLLY *Traite technique d'hematologie* Maloine, édit Paris (1923).

An excellent morphological description of the bursa Fabricii. (In French.)

KINUGASA, SHIGERU · *Functions of the cortex and the medulla of the thymus, especially their relation to the sexual glands.* Keijo J Med. 1, 1 (1930).

A monograph (48 pages, 38 plates, 22 tables, 45 references) concerning the experimental morphology of the thymus, especially the influence of castration and the precocious induction of puberty by pituitary extracts

KLOSE, H., *Chirurgie der Thymusdruse* In Neue Deutsche Chirurgie Ed by P von Bruns Ferdinand Enke, Publ, Stuttgart 3, 1 (1912)

A monograph (283 pages, 104 illustrations, numerous references) which gives a detailed account of the morphology, physiology and pathology of the thymus with an excellent, almost complete, bibliography up to 1912 Contrary to what is implied by the title, the surgery of the thymus represents only a small fraction of this excellent review (In German)

LUCIEN, M M, J PARISOT AND G RICHARD *Traité d'endocrinologie Les parathyroïdes et le thymus* Gaston Doin & Cie, Publ, Paris (1927)

A volume (635 pages, 98 illustrations, numerous references) which forms part of a treatise on Endocrinology. The rather extensive section on the thymus discusses pertinent morphologic, physiologic and clinical problems. Now somewhat out of date (In French)

PARK, E. A. AND R D. MCCLURE: *The results of thymus extirpation in the dog with a review of the experimental literature on thymus extirpation* Am. J Dis Child. 18, 317 (1919).

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ROWNTREE, L. G, J H. CLARK AND A. M. HANSON · *The biologic effects of thymus extract (Hanson). Accruing acceleration in growth and development in successive generations of rats under continuous treatment with thymus extract* J A. M. A. 103, 1425 (1934).

A paper (17 pages, 4 figures, few references) concerning the alleged acceleration of growth in succeeding generations of rats treated with thymus extract.

SIRIO, L *Timo e sistema linfoide gli organi linfoidi negli stati di atimismo ed ipertimismo. (Ricerche sperimentali e considerazioni cliniche)* Endocrin. e Sc d Costit 17, 1 (1942)

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WORMS, G AND H P KLOTZ. *Le thymus. Anatomie — Histologie — Physiologie clinique et therapeutique.* Masson & Cie Publ, Paris (1935)

A monograph (152 pages, 65 illustrations, numerous references) concerning the experimental and clinical pathology of the thymus. (In French)

changes reminiscent of CUSHING'S SYNDROME OR THE ADRENOGENITAL SYNDROME. However, in most of these, other endocrine organs are also involved and, on the basis of existing case records, it is difficult to establish to what extent the thymic change was of etiologic importance.

MYASTHENIA GRAVIS is a disease characterized by marked muscular weakness and ready fatigability. It affects especially the muscles of the face, of deglutition and of speaking. The resulting ptosis of one or both upper eyelids, as well as the paralysis of the other facial muscles, produces a very characteristic mournful expression.

The disease is most common among adults, but can appear in children. Its cause is unknown; frequently, but not always, it is associated with thymic enlargement or actual thymomas of the thymocyte-containing type. Removal of such tumorous or over-developed thymuses has sometimes effected permanent cures; hence, it has been postulated that the disturbance is due to an excessive production of some "thymic hormone" However, its etiology must still be regarded as doubtful, since the adrenals are frequently hypoplastic and small round-cell infiltrations ("lymphorrhages") are commonly found in the muscles, while over-development of the thymus is not a constant accompaniment of this malady.

The disease is generally regarded as a disorder of the muscle itself or the myoneural juncture. If this is correct, physostigmine derivatives could help by facilitating cholinergic nerve responses.

TREATMENT

The treatment of choice in all thymic tumors causing local or systemic disturbances, is their SURGICAL removal. If this is impossible, X-RAY OR RADIUM treatment may be attempted, since lymphatic tumors of the thymus are highly sensitive to these rays. Quite recently, CORTICOTROPHIN or CORTICOIDS have been recommended, because under their influence some thymic tumors in man and animals involute rather rapidly and simultaneously the muscular strength may improve. However, only early surgical removal of the tumor can be expected to effect a permanent cure, if the neoplasm is malignant.

In some cases, ephedrine sulfate, a creatinine-free diet and glycine (administered orally) proved beneficial. Physostigmine or its derivatives, particularly prostigmine (*Walker*, 1934) enjoy great popularity, especially if given in combination with atropine (which antagonizes some unpleasant side-effects of physostigmine).

In spite of any treatment, many of these patients die suddenly and there appears to be a close relationship between myasthenia gravis and the so-called thymico-lymphatic state.

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A monograph (103 pages, 43 illustrations, 91 references) concerning transplantation and regeneration of thymus tissue. (In French)

heart, palpitation, exophthalmos, as well as nervous and menstrual anomalies. In *1835, Graves*, in his lectures given at the Dublin Hospital, spoke of this condition but his observations were not published until *1843*. *Basedow's* famous treatise on the subject appeared in 1840. It may be said that all three above-mentioned physicians share, about equally, in the discovery of the condition which, in English-speaking countries, is designated as Graves' and in most other countries, as Basedow's diseases. The earlier observations of *Flajani* (*1802*) in Italy, were not sufficiently precise to justify the practice of referring to the malady as Flajani's disease. The hyperthyroid theory of Graves' disease was formulated by *Paul Julius Moebius* (*1887*) in Germany.

In 1912, *Plummer* described the "toxic adenoma" which he believed to be essentially different from Graves' disease, inasmuch as it was claimed to result in "pure hyperthyroidism," while Graves' disease was supposed to be due to the formation of incompletely iodinized thyroid hormone or "dysthyroidism." It is important to emphasize, however, that even now there is no definite proof that an abnormal thyroid-hormone is ever produced by the gland.

Thyroid Hormone. — As previously stated, *George Murray* was the first to use a thyroid preparation in the treatment of myxedema. In *1891* he prepared a glycerine extract, from sheep thyroids, which proved active upon subcutaneous administration In 1892 it was independently found by *Mackenzie and Fox* that even crude thyroid tissue itself is active when given by mouth.

In 1896 *Baumann* first demonstrated the presence of iodine in the thyroid. Later in the same year he showed that this iodine is intimately associated with thyroid activity. He subjected thyroid tissue to acid or peptic hydrolysis and herefrom obtained a fraction rich in iodine. In it was concentrated the whole activity of the thyroid gland and Baumann called this fraction "*iodothyrin*" (or thyroidin).

In *1899*, *Oswald* prepared a protein, "IODOTHYREOGLOBULIN" (or thyroglobulin), by extracting the whole gland with saline solution and precipitating the pseudoglobulins with saturated ammonium sulfate This preparation contained 7.7% of iodine. Thyroglobulin has a molecular weight of about 700,000 and represents the chief, physiologically active component in the alveoli. The same chemist (*Oswald, 1911*) also succeeded in isolating from the gland DIIODOTYROSINE, a crystalline iodized amino-acid.

A highly active crystalline principle of the thyroid was first prepared by *Kendall* (*1919*), who used alkaline hydrolysis. Believing that the substance was an oxy-indole derivative, he named it "THYROXINE" This compound contained by weight 65% iodine and an amino group. It proved to exert the full physiologic activity of the glandular extracts

In 1926 *Harington* greatly improved the yield of thyroxine obtainable from the thyroid by substituting barium hydroxide for sodium hydroxide as the hydrolytic agent. In the same year he determined the constitution of desiodothyroxine or "THYRONINE" (i.e., thyroxine from which the four iodine atoms [illegible] removed by catalytic hydro- [illegible]

β-[4-(4 hy[illegible] aminopropionic acid The orientation of the four iodine atoms in thyroxine was determined in the following year when *Harington and Barger* synthesized β-[3 5-diiodo-4-(3' 5'-diiodo-4'-hydroxyphenoxy) phenyl]-α-aminopropionic

X

THE THYROID

HISTORIC INTRODUCTION

The gland was first described in detail by the English anatomist *Thomas Wharton* (1656), who gave it the name of "glandula thyreoidea," but until *Haller's* detailed description (1776), it was considered to be an excretory gland with a duct.

Simple Goiter. — The classic writers (e.g., *Pliny*) and several medieval authors *(Marco Polo, de la Vega)* referred to the common occurrence of goiters in certain areas in which the population had to avail itself of "goiter-producing water." Burnt sponge and seaweed, which are rich in iodine, were used against goiter in the Middle Ages. *Proust* (1816) and *Prevost* (1849) were the first to recommend iodine for this purpose, but it was not until *Marine* and *Kimball* carried out their classic experiment in 1916, on the school girls of Akron (Ohio), that iodine was clearly shown to prevent goiter in a population in which, among untreated children, the goiter incidence was high.

Hypothyroidism. — Hypothyroidism had been known even to laymen long before its etiology was understood The typical village moron, so common especially in mountainous regions, has always attracted attention because of his extreme mental retardation, dwarflike stature, stubby nose, thick skin and poorly developed, shaggy hair, which clearly characterized him as a hypothyroid. *Juvenal* (60-140 A.D.) the Roman satirical poet and *Pliny the Elder* (23-79 A.D.) both described goiters. In 1181, *Roger of Palermo* used ground sponges and sea-weeds rich in iodine, to treat this disease, while as early as 1820 *Coindet* treated hypothyroid goiter with iodine.

It was not until 1871, however, that *Hilton Fagge* expressed the view that sporadic cretinism is due to the absence of the thyroid. In 1873, *Sir William Withey Gull* of London first described what he termed a cretinoid condition developing in adult women. Soon afterwards, *W. M. Ord* (1877), a London surgeon, gave the disease the name "myxedema" because of the mucous tissue which infiltrates the afflicted skin areas. In 1879, the brothers *Reverdin* found, in Switzerland, that following total and sometimes even sub-total thyroidectomy for goiter, there appears what they termed "postoperative myxedema." About the same time, the Swiss surgeon *Kocher* described severe loss of weight and debility ("cachexia strumipriva") after such operations

Subsequently, in 1891, *G. R. Murray*, an English physician, administered thyroid to a myxedematous patient who showed a remarkable improvement and lived 28 years in excellent health, under the influence of this therapy. This patient finally died from cardiac failure at the age of 74 *Magnus-Levy* (1895) first noted that thyroid-medication raises the otherwise low B.M.R in hypothyroidism

Hyperthyroidism. — In 1786, the English physician, *Caleb Hillier Parry* described a disease characterized by thyroid enlargement, dilatation of the

degree of their physiologic activity. They are attached to a delicate, reticular basement membrane and surround a central cavity. The diameter of the latter is extremely variable, measuring anywhere between 1 and 300 μ.

The cells of the follicular epithelium are essentially uniform. It is true that some are chromophobe while others (the colloid cells of Langendorf) are strongly eosinophilic and possess a pyknotic nucleus, but these forms appear to represent merely different stages in the life and secretory activity of the same cell type. The Golgi apparatus of the thyroid epithelium is normally situated near the free pole of the cell but may extend towards the base. The mitochondria are usually short and rod-shaped. During the process of secretion, both the Golgi apparatus and the mitochondria show great variations in position and shape but it has not yet been possible to correlate, in a definite manner, the appearance of these organoids with the type of thyroid activity (storage of colloid or hormone secretion). The thyroid epithelium is essentially capable of merocrine, apocrine and holocrine secretion, as judged by the fact that colloid granules may be discharged into the lumen as such or surrounded by part or all of the cell-body.

It is now generally agreed that the COLLOID found within the thyroid follicle is a storage product and contains large quantities of thyroid hormone, which can be utilized when necessary. The colloid itself is usually acidophilic, but in some or all follicles of the thyroid it may become basophilic under certain conditions. A dense, strongly staining, acidophilic colloid is characteristic of a resting thyroid, the follicles of an actively secreting gland tend to contain basophilic, thin colloid. For this reason dilute (poorly staining) basophilic colloid is usually regarded as being in the process of absorption or transference from the follicular lumen into the blood or lymph vessels. Occasionally, at the borderline between the free pole of the epithelial cells and the colloid, small apparently empty spaces, so-called "absorption vacuoles" are found. These have previously been interpreted as due to enzymatic absorption of the colloid but are now recognized to be artefacts produced by the process of fixation in thin colloid.

The so-called INTER- or PARAFOLLICULAR CELLS are solid, slightly acidophilic cell nests found within the stroma between the thyroid follicles. Their cytoplasm frequently contains argyrophilic granules, hence their tinctorial properties permit their delimitation from ordinary follicular epithelia even in tangentially cut, peripheral portions of thyroid follicles in which a lumen is not distinguishable.

The entrance of IODINE into the thyroid has been studied by administering radioactive iodine to experimental animals and then making sections of their thyroids. These sections were then directly applied to photographic plates upon which, through its β-radiation, radioactive iodine makes an imprint (so-called "radio autograph") wherever the element is present. Thus, uptake of iodine by cells and colloid, respectively, can be followed.

The connective tissue STROMA of the thyroid contains numerous lymphocytes, macrophages and sometimes islets of thymus tissue.

The thyroid ARTERIES — one superior and one inferior on each side — endow the gland with a particularly rich blood supply. It is estimated that blood flows through the gland at the rate of about 5 liters per hour. The VEINS form large surface plexuses. From these the superior, middle and inferior thyroid-veins are formed on each side. The former two open into the internal jugular, while the inferior veins enter into the innominate vein.

acid and showed it to be identical with thyroxine (see p. 696).

Anti-Thyroid Drugs. — One of the most recent developments in the study of the thyroid is the discovery of "antithyroid drugs."

In 1928, *Chesney, Clawson and Webster* discovered that rabbits, kept on a CABBAGE diet, more or less regularly developed goiters. Soon after that, *Marine* et al. (1932) noted that prolonged oral administration of cyanides has the same effect; they suspected that the presence of similar compounds in certain plants may be responsible for the thyroid-stimulating effect of such diets. This recalls the earlier work of *Reid Hunt* (1905), who found that thyroid-feeding increases the acetonitrile (methyl-cyanide) resistance of mice.

Subsequently, it was observed that sulfaguanidine (*Mackenzie, Mackenzie and McCollum*, 1941), phenylthiourea (*Richter and Clesbey*, 1942), allylthiourea (*Kennedy*, 1942), and various other THIOUREA derivatives cause thyroid enlargement, accompanied by a decrease in thyroid-hormone production. This was first systematically employed in the treatment of Graves' disease by *Astwood* (1943) who, among several other drugs of this type, found thiouracil particularly effective.

It has also been found recently that RADIOACTIVE IODINE may improve the condition of hyperthyroid patients. The thyroid has a special affinity for iodine and if the latter is radioactive, it tends to cause local destruction, thus diminishing the function of the gland (*Hamilton and Soley*, 1942; *Hertz and Roberts*, 1942).

Much work is now in progress in an effort to determine which of these antithyroid drugs will prove most beneficial and least toxic; they certainly offer much promise for the future therapy of hyperthyroidism.

NORMAL MORPHOLOGY

ANATOMY

In man, the thyroid is a highly vascular, brownish-red organ consisting of two lateral lobes united by a transverse portion, the isthmus. The gland is adherent to the trachea and larynx so that it follows the movements of the latter during the process of swallowing. The lateral thyroid lobes extend backwards to the sides of the pharynx and esophagus Anteriorly, the gland is covered only by a thin layer of fascia and thin muscles so that it may readily be palpated, especially if it is somewhat enlarged

The shape of the thyroid is subject to great variations. It is only remotely reminiscent of a shield (thyreos = shield) and resembles more closely a letter "H." The isthmus may be thin or entirely absent and occasionally a so-called pyramidal process or "lobe of Lalouette" protrudes craniad from the isthmus.

The weight of the thyroid varies between 20 and 40 gm in adults and is generally somewhat greater in women than in men. The greatest transverse diameter of the whole gland is approximately 5 cm, about the same as the vertical height of the lateral lobes. The antero-posterior diameter of the lateral lobes measures about 2 cm. and that of the isthmus about 0.5 cm; the width of the isthmus is 1-2 cm (See p 539.)

HISTOLOGY

The fundamental unit of the thyroid parenchyme is the thyroid follicle (follis = a bellows). It is lined by a single layer of EPITHELIUM whose cells are of variable height, depending upon the

The thyroid also contains an ample supply of LYMPHATICS; these surround *the follicles* and may contain colloid material, similar to that seen in the follicular lumen. The main efferent lymphatics *follow the thyroid arteries.*

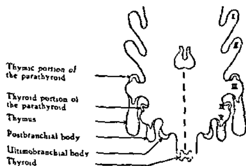
The NERVES of the thyroid are derived from the middle and inferior cervical ganglia of the sympathetic. They accompany the blood vessels and consist mainly of unmyelinated fibers. Their terminal branches reach to the base of the follicular epithelium.

COMPARATIVE MORPHOLOGY

The size and shape of the thyroid differs greatly in the various animal species. Thus for instance in the dog, *there is no isthmus;* in birds, which also *have two separate thyroids,* the glands are situated within the thoracic cavity. In certain animal species (e.g., *rat,* dog) individual small thyroid follicles are lined by a stratified squamous epithelium; they resemble the Hassall bodies of the thymus.

EMBRYOLOGY

The thyroid develops early in the human embryo (at the 1.37 mm. stage). It forms originally solid cords, which later become canalized and subdivided into follicles. The gland arises from one median and two lateral outgrowths of the primitive pharynx. The median primordium arises at the level of the first pharyngeal pouches, from a region which is permanently marked in the adult by the so-called "foramen cecum," a groove at the root of the tongue. From here the thyroglossal duct protrudes downward and forms the most important part of the thyroid primordium. *Parts of the thyroglossal duct may persist during postnatal life and give rise to the pyramidal lobe or even to lingual goiters* The lateral primordia grow from the ventral border of the 4th pharyngeal pouches, they are comparatively unimportant in man in whom apparently most, if not all, of the thyroid tissue is formed from the median primordium. In the human being, significant amounts of colloid are not formed before birth.



Embryology of the branchial organs

THEORIES CONCERNING THE HISTOPHYSIOLOGY OF THE THYROID

As a typical *storage-gland,* the thyroid may secrete either *into the lumen of the follicles (storage) or into the* perifollicular blood vessels and lymphatics (incretion). It is generally assumed, although without definite proof, that most if not all the thyroid secretion is eventually discharged into the blood capillaries and little if any is carried away through the lymphatics.

Reabsorption of stored colloid occurs when the demand exceeds the amount directly increted The hormone in the colloid is probably first hydrolyzed, to an absorbable form, by a proteolytic enzyme. There is some uncertainty as to whether the colloid is discharged into the blood through the cells themselves or through pre-existent channels *between the cells.*

It is possible that the different follicles and even the individual cells in any one *follicle* act intermittently, so that a cycle of secretion results, which is interrupted by periods of rest. This may account for the fact that in almost any normal thyroid, certain follicles are evidently much more active than others.

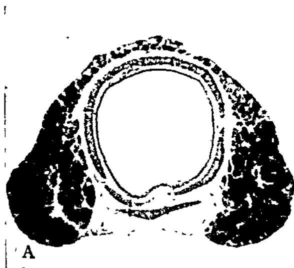
Using the radioautograph technic (cf. p 693), it was found that the





Normal thyroid (Man). — A. and B. Note irr[…] ated, brittle (and hence, fragmented) colloid […] vacuoles" (artefact !) are visible in the coll[…] immature, small follicles, similar to those found in the embryonic thyroid […]

(Courtesy of Dr W Bonin)





Radio-autograph of the thyroid. — A Radio-autograph of the thyroid of an adult rat injected with I_{131} The method employed consists in covering the sections themselves with a photographic gelatin emulsion which is developed after a sufficient exposure to the rays of the radioactive elements in the sections Finally the section is stained through the gelatin coating and mounted in the usual manner — B Higher magnification of the same thyroid Below tracheal cartilage ring at the top the thyroid vesicles, which contain numerous dark dots corresponding to the radioactive iodine

(Courtesy of Dr L -F Bélanger)

GENERAL PHARMACOLOGY OF THE THYROID HORMONE

STANDARDIZATION

Analytic Methods. — Dried thyroid tissue, or thyroid extracts, may be assayed chemically by determining their *thyroxine-iodine content.*

Bioassay. — The biologic evaluation of thyroid preparations is based on their ability to elicit one of the specific, physiologic effects of the hormone. The *reliability of these technics is somewhat* limited by the individual variability in the response to a certain dose, and because only few of the recommended tests are really entirely specific for *thyroid hormone.* The *most commonly* used bioassay methods are based on one of the following actions of the hormone:

(1) Oral administration of thyroid *hormone to the guinea-pig or rat causes* a rise in OXYGEN CONSUMPTION which persists about three days. Essentially the same effect of the hormone is measured when CARBON DIOXIDE PRODUCTION in the mouse is used as an indicator.

(2) The SENSITIVITY TO OXYGEN DEFICIENCY is augmented by thyroid hormone in the rat; this can also serve as a basis for bioassay.

(3) The most sensitive technics are those in which the effect of thyroid hormone on METAMORPHOSIS is selected as an indicator of potency. These determine the minimum amount of hormone necessary to accelerate the metamorphosis of the tadpole into the frog (*Gudernatsch* test), or to cause transformation of axolotls (see p 706) into amblystomas

(4) The ACETONITRILE RESISTANCE of the mouse is greatly augmented by thyroid hormone this is the basis of the *Reid Hunt* test

(5) A very satisfactory procedure is to determine the RESPONSE OF MYXEDEMATOUS PATIENTS to thyroid medication but this technic is, of course, not practical for large scale experimentation.

PHARMACOLOGY OF THYROID HORMONE DERIVATIVES

l-THYROXINE closely imitates all actions of the functional thyroid. It is undoubtedly the active principle of the gland. Among the substances now available in pure form *it possesses the* greatest biologic activity. Yet, as we shall see later, free thyroxine is not necessarily the form in which the hormone circulates in the blood.

DIIODOTHYRONINE (which is identical with thyroxine but for the loss of 2 iodine atoms) is only about 1/40 as active as thyroxine; however, it has the advantage over the latter of being much *more soluble and hence, better absorbed* when given by mouth.

THYRONINE (which represents a thyroxine deprived of all its iodine atoms) is entirely devoid of thyroid hormone *activity*

TETRABROMOTHYRONINE (which is the bromine analogue of thyroxine) possesses some, though slight, thyroid hormone potency. This may be ascribed *to the close chemical relationship* between the two halogens, iodine and bromine.

TYROSINE, the amino-acid which acts as the mother substance of the hormone, *is entirely inert.* Even DIIODOTYROSINE exhibits only a trace of activity, although by enzymatic synthesis, diiodotyrosine-peptone can be converted to an active protein.

THYROGLOBULIN possesses a much greater physiologic potency than corresponds to its thyroxine content. Its potency is more closely related to its iodine content.

VARIOUS IODINIZED PROTEINS (casein, serum protein, etc.) are likewise endowed with some thyroid-hormone activity

RADIOACTIVE THYROXINE (in which two of the iodine atoms are radioactive) has been prepared by *Joliot et al.* (1944) It lends itself particularly well to studies concerning the metabolism of thyroxine, since its presence in blood and tissues is easily detected, due to its *radioactivity. It exhibits a special tend*ency to penetrate into the liver and to be stored there. Subsequently, large amounts are eliminated into the bile and presumably reabsorbed again (*Leblond*)

iodine is first taken up by the epithelium and subsequently deposited in the colloid. In iodine-deficient animals, and after thyrotrophin injection, the transfer of radio-iodine into the colloid is much accelerated, while after hypophysectomy, it is greatly delayed. It was concluded that thyroglobulin is formed in the cells and then stored in the colloid, the rapidity of this process being directly proportional to the activity of the gland.

(For interpretation of hormone production see: Biogenesis, p. 698.)

CHEMISTRY OF THE THYROID

CHEMICAL COMPOSITION OF THE GLAND

The chemical composition of the thyroid is not sufficiently different from that of other organs to deserve any detailed description, except as regards its iodine and thyroid hormone content. The latter will be discussed in connection with the Chemistry below and Biogenesis (p. 698) of the Hormone.

Suffice it to state here that the total iodine content in the normal human thyroid is approximately 10-15 mg. (2 mg./gm of dry tissue) or about 20% of the entire iodine supply of the body, although by weight the thyroid represents only 0 05% of the body weight An iodine content of less than one mg./gm. of dry tissue is definitely abnormal. In parenchymatous (simple or exophthalmic) goiter it may drop to 0.25 mg /gm. or less. The colloid, which stores the hormone, usually contains 2 to 20 times as much iodine as the cells (the two can be separated for analysis by centrifugation).

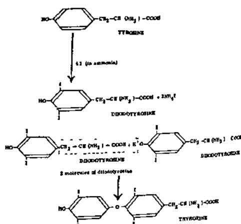
CHEMISTRY OF THE THYROID HORMONE

The general characteristics of IODOTHYRIN, IODOTHYREOGLOBULIN, DIIODOTYROSINE and THYRONINE, have already been mentioned in the Historic Introduction. (See p 691.)

It will be noted that both diiodotyrosine and thyroxine are amino-acids and as far as is known, these and thyroglobulin are the only iodine-bearing organic compounds in the thyroid.

THYROXINE forms fine, colorless sheaves and rosettes of crystal needles, which decompose at the melting point with the evolution of iodine. The compound is comparatively stable to alkali, with which it forms two series of salts because of its two (phenolic and carboxylic) acidic groups. When isolated from the gland by the usual methods it is optically inactive, but by separating the isomers it was found that only *l*-thyroxine possesses physiologic activity. It probably exists in the gland in this levorotatory form since it may be obtained from the thyroid as such, by gentle enzymatic hydrolysis. Free thyroxine is comparatively insoluble in most solvents but an injectable, aqueous solution may be prepared from its sodium salt.

The following scheme was originally proposed by *Harington* (1927) as the possible biological origin of thyroxine and shows the relationship between this amino-acid and its precursors·



The validity of this scheme may now be regarded as established by evidence which has accumulated in recent years

Doubt that thyroxine is the native hormone is based upon the observation of discrepancies between its physiologic activity and that of thyroid substance. *It has also been questioned that such a highly insoluble compound as thyroxine would circulate in the* blood, as such. It remains to be shown, however, whether the differences in the actions of thyroxine and thyroglobulin are not merely due to the relative insolubility of the former. Several prominent workers in this field (*Harington, Taurog and Chaikoff, Leblond*) provided evidence in support of the view that thyroxine itself is the circulating hormone.

Fate of Thyroid Hormone in the Body. — It has been estimated that the *normal human thyroid produces the equivalent of 0.3 - 0.5 mg. of thyroxine per day.* Since in the complete absence of thyroid tissue, about 0.5 mg. of thyroxine per day are required to maintain metabolism at a normal level, it has been concluded that approximately this amount is "used" daily under physiologic conditions. It is not known *to what extent this hormone "utilization" is due to excretion, combustion or inactivation by conjugation with other substances.* The comparatively great thyroxine sensitivity of thyroidectomized individuals, led to the belief that the thyroid itself participates in the inactivation of its own hormone

Mechanism of Thyroid Hormone Action. — The main effect of the thyroid hormone is apparently to increase the oxidative processes in the tissues *In this respect, it appears to act as a catalyst, or at least as an activator of, respiratory cell-enzymes.* This action is direct and not mediated through the nervous system, since excised tissues of hyperthyroid animals exhibit an excessive, while those of hypothyroid animals have a subnormal tissue respiration rate in vitro It is true that the direct addition of thyroxine to excised tissues causes no clear-cut, *immediate rise in their metabolism, but this may be due to the delayed activity of this hormone, especially since the more soluble and hence, more immediately utilizable* thyroglobulin appears to be effective under similar conditions. The slow activity of thyroxine is one of its very characteristic features. For instance, upon administration of a single dose, the rise in B.M.R. commences only after about 7 hours and reaches a maximum after one or two weeks. Even two months after a single injection, however, the B.M.R. may still be above normal.

As we shall see later, there are some effects of thyroid hormone (e.g., prevention of deficiency cell formation in the hypophysis of the thyroidectomized rat, metamorphosis, cardiotrophic action), *which cannot be reproduced by other agents* conducive to a marked rise in B.M.R. Hence, it is not admissible to consider all thyroid hormone actions as secondary to the stimulation of tissue metabolism

Different Kinds of Thyroid Hormones. — There is no conclusive evidence to prove that the thyroid normally produces several hormones with quantitatively or qualitatively different actions *It has been claimed that in thyroidectomized rats, different thyroid* preparations may predominently stimulate the B.M.R. or the pulse rate. However, the presence of impurities in such preparations may account for this apparent qualitative difference; furthermore, the normal thyroid contains thyroglobulin, diiodotyrosine and thyroxine *which possess different degrees of thyroid hormone potency. It is conceivable* that all three of these compounds are discharged into the blood stream under physiologic conditions and that their relative proportion in the circulating blood is subject to variations.

MODE OF ADMINISTRATION

The ORAL ROUTE is the most popular, simplest and cheapest method of administering thyroid-hormone to patients with hypothyroidism. It can best be given in this manner as U.S.P. "desiccated thyroid" tablets (1/10 to 2 grains or 6 to 120 mg.). These consist of cleaned, dried, defatted and powdered thyroid glands of edible animals. It is important to emphasize that the U.S.P. specifies a higher potency than the B P. The doses recommended in this book refer to the U.S.P. product which according to the pharmacopeia must contain 0 2% iodine. Thyroxine is also available in tablet form, but because of its comparative insolubility, its absorption from the intestinal tract is subject to great variations. (See also, pp 741, 742.)

For INTRAVENOUS administration, thyroxine is available in the form of its water-soluble sodium salt, in ampules containing 1-10 mg. Since, irrespective of the method of administration, the action of the hormone is slow, intravenous injection of thyroxine is hardly ever justifiable.

SENSITIZATION AND DESENSITIZATION

There is no convincing evidence to prove that upon continued treatment with thyroid hormone, the organism would either become abnormally sensitive or unusually resistant to it. Normal individuals are much less sensitive to thyroid-hormone overdosage than hypothyroid animals or human beings. Adipose, but otherwise normal, patients may tolerate up to 30 grains of desiccated thyroid per day without an increase in pulse rate or any other striking manifestations of hyperthyroidism The cause of this resistance is not known, but perhaps the normal thyroid can destroy an excess of its hormone True antihormones are not formed against thyroxine The gradual increase in its effect, which is often observed in the course of prolonged treatment, is merely due to the slowness of its activity. The maximal action of the first dose may not be fully manifest for weeks, when its effect is added to that of subsequent doses (phenomenon of "cumulative activity").

THEORIES CONCERNING THE THYROID HORMONE

Biogenesis. — Since we do not know as yet what hormone (or hormones) the gland produces under physiologic conditions, it is not surprising that we are still ignorant of the mechanism of thyroid-hormone biogenesis. It is probable, however, that with the aid of inorganic iodine, tyrosine is transformed into diiodotyrosine and that subsequently two molecules of the latter are condensed to form thyroxine. Diiodotyrosine and thyroxine are then used as such in the synthesis of thyroglobulin through peptide-linkage This view is supported by the fact that, in vitro, the highly active thyroglobulin may be split into the less active thyroxine and the almost inactive diiodotyrosine as well as other non-iodinized amino-acids. In this connection, it is also noteworthy that, on standing in alkaline solution, diiodotyrosine is partially converted to thyroxine in vitro. Upon treatment with iodine, even casein, which contains much tyrosine, can be partially transformed into thyroxine. It has actually been possible to isolate the latter from the iodinized casein. In agreement with this interpretation, diiodotyrosine, thyroxine and thyroglobulin are found in normal thyroid tissue

It is now generally believed that through some such mechanism as that described above, thyroglobulin is formed in the thyroid and that the hormone is stored as thyroglobulin in the colloid of the vesicles It is debatable, however, whether thyroglobulin itself is the hormone or whether it is converted into a simpler polypeptide when released into the circulation.

ficult to understand, why rats and guinea pigs (unlike mice) become especially sensitive to acetonitrile poisoning when treated with thyroid hormone.

Temperature. — The body temperature is diminished by thyroidectomy and slightly raised by thyroid hormone overdosage. The hypothermia elicited by exposure to severe cold or by injection of barbiturates can be prevented by desiccated thyroid, while the fever caused by cocaine or tetrahydronaphthylamine is accentuated by it.

Basal Metabolism. — The basal metabolic rate (B.M.R.) is the oxygen consumption (or CO_2 production, or heat production) under fasting conditions (to eliminate specific dynamic action of food), absolute rest (to eliminate increased caloric requirements for muscular work) and at normal room temperature (to eliminate variations in caloric requirements for the maintenance of normal body temperature). There is no close correlation between body weight and B.M.R. but extensive experimental work shows that normally the B.M.R. runs closely parallel with the body surface. Deviations of $\pm 10\%$ are considered to be within the normal range. After complete thyroidectomy, the B.M.R. drops to about -40% while excessive amounts of thyroid hormone may raise it up to $+100\%$.

It is generally assumed that its influence upon tissue oxidations is the most important function of the thyroid and that most of its other effects are secondary to it. This is not entirely correct. Agents which depress (hypophysectomy, hibernation) or increase (dinitrophenol, acute infections with high fevers) metabolism do not completely imitate hypo- and hyperthyroidism respectively, nor can the effects of thyroidectomy be entirely prevented if the B.M.R. is raised by agents other than thyroid hormone.

In the normal adult, one mg. of thyroxine intravenously (or 1 grain of desiccated thyroid per os) causes a 2.8% rise in the B.M.R. and larger doses increase metabolism proportionately. The subnormal B M R. of thyroidectomized individuals, however, is much more intensely raised by the same dose of the hormone. This is merely one example of what appears to be a general law in endocrinology namely, that the same dose of the hormone is much more effective in causing restoration to normal, in the event of hormone deficiency, than it is in producing a rise above the normal level.

Carbohydrate Metabolism. — Thyroidectomy increases glucose tolerance while thyroid hormone diminishes it and causes a tendency towards alimentary glycosuria. It is assumed that the decreased glucose-tolerance of hyperthyroidism is due to a diminished ability to deposit glycogen in the hepatic cells, since thyroid hormone depletes the liver-glycogen stores (without significantly affecting the glycogen content of skeletal muscles). Accelerated glucose absorption from the intestine and damage to the Langerhans islets of the pancreas may also play a rôle in this phenomenon. The liver glycogen depleting action of thyroxine is inhibited by the vitamin-B complex.

Thyroidectomy has effectively been employed in combatting spontaneous diabetes, but since the introduction of insulin, this type of therapy, is, of course, no longer practised.

Lipid Metabolism. — Thyroidectomy causes a rise in the total lipid, and especially in the cholesterol content, of the blood. This effect is particularly obvious in man but not clearly demonstrable in all animal species (e g., rat). Thyroid-hormone overdosage tends to depress the blood-cholesterol level, but not as markedly as thyroidectomy increases it. In a thyroidectomized individual, however, thyroid hormone readily restores the blood cholesterol to normal. There is no definite evidence that fat deposition is enhanced by thyroid deficiency, since thyroidec-

EXPERIMENTAL PHYSIOLOGY OF THE THYROID

EXPLANTATION OF THE THYROID

Thyroid tissue tends to retain many of its typical morphologic and biochemical characteristics when cultured in vitro. It can also be grown in organ culture: that is, upon artificial perfusion of the entire isolated thyroid.

It is noteworthy that in vitro, the thyroid takes up large amounts of iodine from the perfusion fluid, especially if the gland is hyperplastic. Conversely, it discharges thyroid hormone into the perfusion fluid.

TRANSPLANTATION OF THE THYROID

Autoplastic and, to a lesser degree, homoplastic (but not heteroplastic) transplantation of human thyroid tissue has often been successful; after some time, however, the homoplastic transplants especially tend to undergo involution. Hence, except under very rare circumstances, oral thyroid medication is preferable.

Animal experiments have clearly proven, however, that the transplanted thyroid may retain its physiologic activity and almost indefinitely prevent hypothyroidism after thyroidectomy.

TECHNIC OF THYROIDECTOMY

In most animal species, the surgical intervention of thyroidectomy is not very difficult but careful attention must be given to the parathyroids, which in many animal species are enclosed in the thyroid. Their removal with the thyroid, results in rapidly fatal tetany and makes it impossible to observe the consequence of pure thyroid deficiency. If the parathyroids are preserved (which in some species necessitates their enucleation from the thyroid and transplantation into another tissue), thyroidectomy is compatible with the maintenance of life.

EFFECTS OF THYROIDECTOMY AND THYROID HORMONE TREATMENT

State. — The APPEARANCE of experimental animals following thyroidectomy resembles that of hypothyroid patients (see: pp. 724-739). They are stunted, sluggish and, if the operation is performed early in life, show evident signs of cretinism. Excess thyroid hormone administration, on the other hand, causes marked loss of weight and great excitability.

The RESISTANCE TO VARIOUS TYPES OF NON-SPECIFIC DAMAGING AGENTS (infections, intoxications, trauma, etc.) is greatly diminished both by thyroidectomy and by thyroid hormone overdosage; this is probably merely a consequence of the resulting general systemic damage. It is especially noteworthy, however, that thyroidectomized animals — by virtue of their lowered metabolic rate — become more resistant to ANOXIA (excess CO_2 in the atmosphere, or reduced barometric pressure) than intact controls. Since their caloric requirements are low, they also become more resistant to prolonged UNDERNOURISHMENT. Conversely, thyroid hormone overdosage renders the organism unusually sensitive to anoxia and undernourishment.

Resistance to COLD is considerably decreased in the absence of the thyroid, because one of the most important physiologic defence mechanisms against low temperatures — namely, the increased heat production by a rise in oxidative processes — is severely impeded. Normally, excess thyroid hormone production facilitates these adjustments in animals exposed to cold.

The fact that thyroid hormone raises the resistance of mice to ACETONITRILE poisoning has been used as the basis of a bioassay technic (see: Bioassay, on p. 697), but the underlying mechanism is still inexplicable. It is also dif-

in the general, catabolic effects of the hormone.

The metabolism of OTHER ELECTROLYTES reveals no noteworthy specific disturbances in experimental hypo- or hyperthyroidism.

Thyroidectomy causes a definite tendency toward the accumulation of WATER and "deposit protein" in the intercellular spaces. This effect is counteracted by thyroid-hormone administration. — Conversely, in certain disturbances of water metabolism which are conducive to edema, and especially in the nephroses, thyroid medication causes marked diuresis; thus it counteracts the edema tendency, even though there is no hypothyroidism.

Metabolism of Other Substances. — In growing individuals, hypothyroidism decreases the blood PHOSPHATASE concentration and thyroid-hormone treatment restores it to normal.

Growth and Bone Structure. — Thyroidectomy if performed in immature, growing animals, retards the development of the skeleton and causes dwarfism, mainly as a result of abnormal ossification at the junction cartilages of the long bones. Small doses of thyroid hormone may occasionally accelerate skeletal development, while high doses definitely interfere with somatic growth, probably because of their general, systemic toxicity.

In the adult animal, neither thyroidectomy nor thyroid hormone overdosage exert as marked an effect upon the skeleton as in growing individuals, but pronounced experimental hyperthyroidism is always accompanied by considerable osteoporosis.

Blood Picture. — Thyroidectomy may occasionally cause some degree of anemia, while thyroid-hormone overdosage tends to produce reticulocytosis, by stimulating the blood-forming organs.

Cardiovascular System. — Thyroidectomy decreases cardiac size and pulse rate, while thyroid hormone administration produces cardiac hypertrophy and tachycardia, accompanied by an increase in the systolic blood pressure and by peripheral vasodilatation. (See also pp. 735, 736, 752.) The increased cardiac output may, in part, represent an adjustment to the calorigenic action of thyroid hormone, but there must also be some direct cardiac effect of the hormone since the isolated heart of hyperthyroid animals continues to exhibit an increased pulse rate in vitro. This cardiotrophic effect is apparently independent of the nervous system, since it is not abolished by denervation. The cardiovascular lesions (periarteritis nodosa, myocarditis) normally elicited by certain anterior-pituitary and corticoid preparations in the rat, are aggravated by thyroxine and attenuated by thyroidectomy.

Thyroidectomy (or anti-thyroid-drug treatment) has been advocated as a palliative measure in congestive heart-failure and angina pectoris, even if the patient was not suffering from hyperthyroidism. However, the results hardly justify such drastic interventions, especially since the possible detrimental effects upon the heart of myxedema, must also be kept in mind.

Lymphatic Organs. — Following thyroidectomy, the lymphatic organs, notably the lymph nodes, thymus, spleen and bone marrow, usually show moderate involution. Treatment with low doses of thyroid hormone stimulates the growth of these organs; large doses, however, presumably through their effect upon the adrenal cortex (see section on General-Adaptation-Syndrome), cause pronounced involution of the thymico-lymphatic system.

Respiratory Organs. — Neither thyroidectomy nor thyroid-hormone administration exert any outstanding, specific effects upon the respiratory organs of mammals. It is noteworthy, however, that the involution of gills and

tomized animals exhibit no tendency towards general adiposity.

Protein Metabolism. — Thyroidectomy decreases, while thyroid-hormone overdosage increases the urinary elimination of nitrogen. Thyroid hormone also causes marked creatinuria with a reduction of preformed creatinine and an increase in the excretion of ammonia and uric acid. All these changes are indicative of an increased destruction of (exogenous and endogenous) proteins.

Salt and Water Metabolism. — IODINE METABOLISM is most intimately connected with thyroid function. Not only is iodine indispensable for the synthesis of thyroid hormone, but the latter in turn exerts an important influence upon iodine distribution in the tissues.

The total iodine content of the normal human body is approximately 50 mg.; of this the thyroid contains about 10-15 mg (50 mg./100 gm. of fresh tissue) and the muscles 25 mg. (0.03 mg./100 gm of fresh tissue).

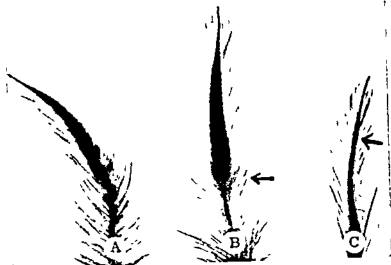
Iodine is mainly absorbed by the intestine and excreted through the kidneys. The minimum daily iodine requirement of adults is about 25γ, but it is best to supply 100-200γ. The methods for the determination of iodine in biologic materials are rather unreliable, but it is estimated that about 20 to 70γ/day are excreted, through the urine. It is likely that most of the iodine so excreted comes from metabolized thyroid hormone. Only part of the iodine, liberated from the decomposition of the hormone, is excreted, some being repeatedly utilized for resynthesis in the thyroid.

The iodine content of the thyroid has been discussed above (p 696) under "Chemical Composition of the Gland" Of the total blood iodine about 2 4 to 5.5γ/100 cc, the major part (4 to 10γ/100 cc.) is in the plasma. It has been customary to distinguish between organic and inorganic iodine, on the basis of its solubility in alcohol and acetone, but the pertinent methods are not very reliable. *Salter* separates plasma iodine into two fractions, one ultrafiltrable (not precipitable with protein precipitants, probably inorganic iodides), and the other not ultrafiltrable (appears to be attached to the plasma proteins since it precipitates with them). This latter fraction may be further subdivided into "thyroxine-like" and "diiodotyrosine-like" components The thyroxine-like fraction represents approximately ⅓ of the total blood iodine. It is usually assumed that about 0.5 mg. of thyroxine iodine is present in the 5 liters of blood of an average normal adult, but this figure is probably too high.

Thyroidectomy decreases, while thyroid-hormone administration increases, the blood iodine in animals and man The excretion of iodine is also diminished by thyroidectomy. Administration of KI increases the ultrafilterable and nonprecipitable (inorganic) blood iodine, but does not significantly affect protein-bound iodine in normals.

CALCIUM AND PHOSPHORUS elimination are decreased following thyroidectomy, but this rarely gives rise to a marked retention of these elements, since the intake is correspondingly low as a result of the decreased appetite.

Conversely, thyroid hormone overdosage causes a pronounced increase in the fecal (less in the urinary) excretion of calcium. This is only partly accounted for by over-eating and increased intestinal peristalsis. Toxic doses of thyroid hormone cause retardation, or cessation, of skeletal growth (see p. 703). In adults, there may be pronounced osteoporosis due to "smooth absorption," that is, without any marked proliferation of osteoclasts This helps to distinguish the process from hyperparathyroidism which leads to osteoclastic bone absorption. It is doubtful whether the effect upon the bones is specific or whether it merely represents participation of the skeleton



Effect of thyroidectomy upon plumage. — A. Normal neck-feather of brown leghorn cockerel, entire feather brownish gray. — B. Similar feather in which the part below the arrow (light) had grown after thyroidectomy. — C. Similar feather in which only the tip (black) above the arrow grew before thyroidectomy.

changes Excessive doses of thyroid hormone induce a rapid and almost continuous moulting of the feathers in birds, and of the skin in snakes

Urinary System. — Thyroidectomy diminishes, while thyroid hormone overdosage increases, the size of the kidney. This change in gross size is probably secondary to the general metabolic stimulation caused by thyroid hormone. It is accompanied by enlargement of both the glomeruli and the epithelial components of the renal parenchyme. The nephrosclerosis normally produced in the rat by anterior-pituitary extract or mineralo-corticoids is aggravated by simultaneous treatment with thyroid hormone.

Accessory Genital Organs. — Thyroidectomy, as well as thyroid hormone overdosage, cause involution of the accessory sex-organs, both in the male and in the female. This is probably due to the non-specific damaging effect of either procedure, which elicits a general-adaptation-syndrome with an accompanying decrease in gonadotrophin production and consequent gonadal atrophy. There is no conclusive evidence to indicate that the thyroid acts upon the accessory sex-organs directly, without the intermediary of the gonads

Sexual Cycle. — The female sexual cycles become irregular or give way to continuous diestrus in animals, and amenorrhea in women, following thyroidectomy or severe thyroid-hormone overdosage. Here again the effect is mediated by the gonads. It is noteworthy that thyroidectomy tends to produce prolonged luteal phases reminiscent of pseudopregnancy. Curiously, and rather inexplicably, thyroid hormone is often beneficial in the therapy of diverse disturbances of menstruation and even in female sterility.

Pregnancy and Lactation. — Thyroidectomy during pregnancy is compatible with the continuance of gestation, but previously thyroidectomized animals rarely become pregnant because of the accompanying changes in the sex organs. Thyroid-hormone overdosage may cause abortion, but comparatively large quantities are tolerated by pregnant animals

Both thyroidectomy and thyroid-hormone overdosage tend to diminish the milk production of lactating animals.

Hibernation. — Thyroidectomy delays while thyroid hormone treatment accelerates, the awakening of hibernating animals. This effect of the hormone is probably due to stimulation of metabolism.

Metamorphosis. — The metamorphosis of amphibia is strictly dependent

the development of lungs in amphibian larvae (and in the axolotl) are induced by thyroid-hormone preparations as part of their metamorphosis-stimulating effect.

Muscles. — Thyroidectomy usually decreases muscular strength without causing any prominent morphologic changes in the musculature. Treatment with large doses of thyroid hormone is frequently followed by a dramatic loss of muscular strength (*reminiscent of mild myasthenia*), which is due to muscular atrophy and to degenerative changes in the striated muscle fibres; it is accompanied by creatinuria and a low creatine content of heart and skeletal musculature.

Nervous System and Sense Organs. — Thyroidectomy impedes the development of intellect, so that a cretinoid condition is produced even in animals, if the operation is performed at an early age. In adult animals, thyroidectomy also decreases, while thyroid-hormone overdosage increases the total activity of the brain, as judged by electroencephalographic criteria The great motor excitability and the tremor of hyperthyroid animals is in sharp contrast to the sluggishness which follows thyroidectomy.

The effect of the thyroid upon the vegetative nervous system is less clear-cut, but in general it appears that thyroid hormone stimulates the excitatory nerves of the various organs, irrespective of whether these are supplied by the vagus or the sympathetic system.

Thyroid hormone does not tend to cause exophthalmos in animals, indeed it usually counteracts the exophthalmic action of hypophyseal extracts (see . Hyperthyroidism, p. 757).

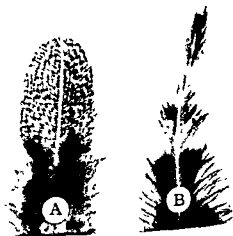
Digestive System. — Thyroidectomy tends to decrease both the secretory and the contractile activity of the gastrointestinal tract, while thyroid-hormone administration has opposite effects

It should also be mentioned that mild hyperthyroidism tends to cause some measure of splanchnomegaly with an increase in the size of the liver and pancreas. The metabolic functions of the liver, on the other hand, are impeded by both thyroid deficiency and overdosage (see: Carbohydrate Metabolism, p. 701).

Skin. — Thyroidectomy tends to cause peripheral vasoconstriction which makes the skin cold; usually there also is some hyperkeratosis and deficiency of hair growth. Actual myxedematous skin-changes are comparatively rare in thyroidectomized animals, but there can be trophic lesions in the nails.

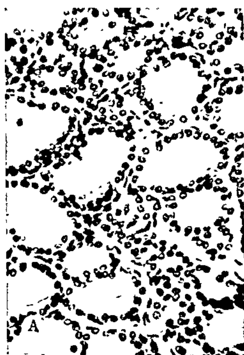
In rabbits and cats there may be alopecia and loss of hair-pigment following treatment with excessive doses of thyroid hormone.

In birds, the feathers often undergo marked abnormalities of pigmentation under the influence of thyroidectomy or thyroid-hormone overdosage The specific character of these pigment anomalies is partly dependent upon hereditary factors, since various strains of birds respond with different color



Effect of thyroidectomy upon plumage. — A. Wing coverts of normal, female silver dorking — *B. Wing coverts* of female silver dorking after thyroidectomy Note change in shape and coloration of feather.

STIMULI INFLUENCING THE STRUCTURE OF THE THYROID

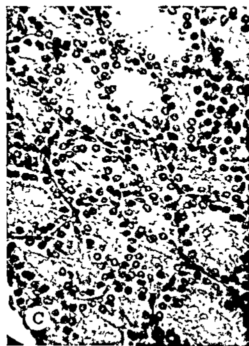




Extirpation of Endocrine Glands. — HYPOPHYSECTOMY induces thyroid involution in all animals, including man. This is due solely to anterior-lobe deficiency; selective destruction of the posterior-pituitary has no such effect and in hypophysectomized animals only anterior-lobe implants or thyrotrophin enlarge the thyroid

After hypophysectomy, PARTIAL THYROIDECTOMY, exposure to cold, or treatment with thioureas — all of which usually cause marked thyroid hyperplasia — are ineffective. Presumably they all act through the anterior-lobe

ADRENALECTOMY, CASTRATION (in either sex), PANCREATECTOMY, PARATHYROIDECTOMY, PINEAL GLAND EXTIRPATION and THYMUS EXTIRPATION gen-



upon the function of the thyroid. Thyroidectomy prevents the transformation of frog larvae (tadpoles) into frogs, although some somatic growth continues in the absence of the thyroid. This action of thyroid hormone is readily elicited even in hypophysectomized tadpoles. Administration of thyroid can also elicit a precocious metamorphosis in intact tadpoles if treatment is begun at an early age.

A singular application of this phenomenon is represented by the metamorphosis of the axolotl which is normally paedogenetic, that is, it permanently lives in the larval stage. In this condition it is purely aquatic, breathes through gills and has a finned tail. If this animal is fed desiccated thyroid or thyroxine, it metamorphoses into the tiger salamander (Amblystoma tigrinum). Even simple iodine compounds, such as diiodotyrosine, or iodine crystals, can induce metamorphosis in the axolotl or tadpole; this is probably due to transformation of these compounds into thyroid-hormone within the animal's body. The non-specificity of this reaction detracts from its value as a basis for bioassays.

Various Other Effects. — The intestinal ABSORPTION of many food substances is impeded by thyroidectomy and accelerated by thyroid hormone. This may partly be due to the effect of the gland upon intestinal contractility and secretion.

REGENERATION AND WOUND HEALING are markedly impeded by thyroidectomy but not significantly accelerated by thyroid hormone treatment.

THYROID HORMONE CONTENT OF BODY FLUIDS AND TISSUES

Because of the intricacy and inaccuracy of most chemical and biologic assay methods, we know relatively little about the thyroid hormone content of various body fluids and tissues under normal and abnormal conditions.

It is estimated that under NORMAL conditions the human body contains about 14 mg., whole-blood 0.1 mg./L. and the human thyroid 5 mg. of thyroxine — or more properly the equivalent of these amounts in biologic activity. It should be kept in mind that only about 40% of the thyroid iodine is thyroxine iodine, the remainder corresponds to diiodotyrosine (cf. p. 699).

Both HYPOPHYSECTOMY and THYROTROPHIN administration decrease the thyroid-hormone content of the gland; the former because it diminishes hormone production, the latter because it stimulates the discharge more than the storage of thyroid hormone.

THYROXINE feeding causes an approximately equal rise in the inorganic and organic fractions of the blood iodine, while after intravenous administration of thyroxine, only the latter fraction rises.

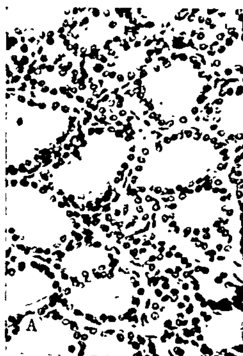
In EXOPHTHALMIC GOITER the hyperplastic thyroid is poor in thyroid hormone, probably because of the greatly accelerated discharge into the blood.

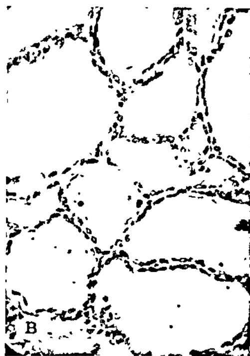
IODINE administration tends to increase thyroid-hormone storage in the gland. This is especially manifest if the thyroid is hyperplastic, for instance after pretreatment with thyrotrophin, or in spontaneous hyperthyroidism.

The THYROID-HORMONE CONTENT OF THYROID TUMORS is usually proportional to the degree of their maturity. Very anaplastic growths may be practically free of hormone.

Thyroid hormone has also been detected in URINE, LIVER, BILE, MILK (particularly following thyroid-hormone administration), MUSCLE, etc. However, there is little in tissues other than the thyroid itself and the venous blood which comes from it. For metabolic studies with radio-thyroxine see p. 697.

STIMULI INFLUENCING THE STRUCTURE OF THE THYROID



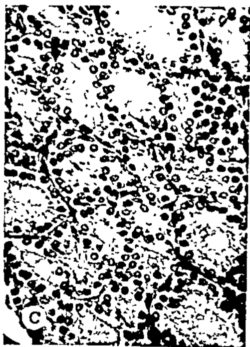


Effect of thyroxin and thyrotrophic hormone

Extirpation of Endocrine Glands. — HYPOPHYSECTOMY induces thyroid involution in all animals, including man. This is due solely to anterior-lobe deficiency; selective destruction of the posterior-pituitary has no such effect and in hypophysectomized animals only anterior-lobe implants or thyrotrophin enlarge the thyroid.

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ADRENALECTOMY, CASTRATION (in either sex), PANCREATECTOMY, PARATHYROIDECTOMY, PINEAL GLAND EXTIRPATION and THYMUS EXTIRPATION gen-



erally remain without any striking effect upon the thyroid.

Hormones. — THYROTROPHIC HORMONE and crude anterior-lobe preparations, which contain it, cause marked thyroid hyperplasia in intact animals and man. Thyrotrophin does not merely prevent the atrophy which otherwise occurs following hypophysectomy, but can actually stimulate thyroid growth, far above normal, in intact animals Under its influence the epithelial lining of the follicles undergoes both hypertrophy and hyperplasia. The individual epithelial cells become high-cuboidal or cylindric, the Golgi apparatus hypertrophies and the colloid is rapidly absorbed from the follicular lumen to be discharged into the blood. Correspondingly, the weight of the thyroid increases and signs of hyperthyroidism ensue In the guinea-pig, for instance, 30-60 minutes after a single injection of thyrotrophin, intracellular colloid granules appear and these are eliminated into the follicular lumen, together with an envelope of cytoplasm (apocrine secretion). 3-20 hours later, there is secretion towards the capillaries adjacent to the basal pole of the cells, that is, in reverse direction.

Thyrotrophin can probably pass through the placental barrier and stimulate the gland of the fetus since in thyroidectomized, pregnant bitches, the offspring often develop parenchymatous goiters

Thyroid hormone, its derivatives and even inorganic iodine, tend to inhibit the thyroid-stimulating action of simultaneously administered thyrotrophin.

THYROID HORMONE and some of its derivatives cause a compensatory atrophy of the thyroid which may become almost as severe as that occasioned by hypophysectomy. It is believed that this compensatory atrophy is due to a decrease in the thyrotrophin production of the anterior-lobe, occurring because of the decreased hormone requirements of subjects treated with large doses of this hormone. However, to some extent, this effect may also be due to a direct action upon the thyroid, since, in hypophysectomized animals, simultaneous treatment with thyrotrophin and thyroxine causes less marked thyroid hypertrophy than treatment with thyrotrophic hormone alone. In these animals, which have no hypophysis, a further diminution by thyroxine of endogenous thyrotrophin production is naturally impossible. Thyroid hormone also inhibits the uptake of iodine by the thyroid.

Diseases. — As may be expected, HYPOPITUITARISM causes involution, while HYPERPITUITARISM usually induces hyperplasia of the thyroid. There is no close correlation, however, between the degree of pituitary derangement — as judged by other symptoms — and the intensity of the thyroid change Probably, interference with thyrotrophin production does not necessarily parallel the derangement in the secretion of other anterior-lobe hormones.

The thyroid lesions associated with various clinical forms of HYPO- and HYPERTHYROIDISM are discussed in the sections devoted to the latter. OTHER DISEASES rarely cause striking and specific changes in the thyroid.

Diet. — The thyroid is especially sensitive to qualitative or quantitative changes in food intake

FASTING OR SEVERE UNDERNUTRITION tend to cause atrophy of the thyroid. This may be interpreted as a useful, compensatory arrangement, since in the absence of a calorically adequate diet, a decrease in B.M.R. (due to thyroid atrophy) is beneficial

The most specific and important dietary factor regulating thyroid development is IODINE. As stated earlier in this section, iodine is indispensable for the synthesis of thyroid hormone.

With inadequate iodine supply, the anterior-lobe of the pituitary produces

excessive amounts of thyrotrophin, in a vain effort to increase the thyroid-hormone supply of the body by over-stimulating the gland which normally produces it. Depending upon experimental conditions, the histologic appearance of the thyroid is somewhat variable on an iodine deficient diet. Usually the picture resembles that produced by thyrotrophin. In most animal species, moderate iodine deficiency results in slight hyperplasia and later, in colloid goiter; *but* further reduction of dietary iodine transforms this *struma* into the parenchymatous type. Subsequent iodine administration induces colloid retention and hence a change to colloid goiter. The degree of thyroid hyperplasia is *inversely* proportional to the iodine content of the gland.

Experiments with I_{131} showed that most of the ingested I is immediately removed from the circulation and deposited in the colloid; the epithelium stores it only in animals previously kept on iodine-rich diets. Through its local cell-destroying effect, radio-I may cause "functional thyroidectomy".

Most other factors conducive to thyroid hyperplasia probably act by creating a relative *iodine* deficiency. Thus certain VEGETABLES, especially cabbage, cauliflower and Brussels sprouts proved to be goitrogenic in the rat and rabbit. If the cabbage is dried in vacuo it loses its goitrogenic potency, whereas boiling with HCl does not modify this activity. Significantly, all these goitrogenic vegetables are rich *in* organic compounds which can liberate cyanides. *It* has also been found that treatment with methyl-cyanide is especially effective in causing thyroid hyperplasia and exophthalmos in the rabbit. It is assumed that the cyanides act because they depress tissue oxidations and thus call for a compensatory *increase* in thyroid activity. This is accomplished by *increased* hypophyseal thyrotrophin production, perhaps through the intermediary of stimuli acting by way of hypothalamic vegetative centers. However, the possibility of a direct action upon the enzymatic synthesis of hormone by thyroid cells must also be considered.

Ingestion of excessive quantities of PROTEIN (especially liver) and deficiency in certain VITAMINS (A, C and D complex) are also slightly goitrogenic.

Nervous Stimuli. — Direct stimulation of the thyroid nerves or denervation of the gland causes no significant change in its function or morphologic appearance, other than such minor variations as can be ascribed to the resulting change in blood supply.

It has been stated that anastomosis between the phrenic and the thyroid nerves sometimes induces goiter by direct nervous overstimulation of the gland, but the results of such experiments are extremely variable and might be due to retrograde stimulation of vegetative brain-centers through the proximal end of the phrenic.

Severe emotional stimuli undoubtedly can elicit Graves' disease (see Hyperthyroidism, p. 747), but it is almost certain that any type of nervous stimulation which causes thyroid enlargement is mediated by excess production of thyrotrophin.

Age. — Histologic evidence suggests that the thyroid begins to function early in the EMBRYO, although at that time its iodine and thyroid-hormone content are still low.

At PUBERTY, there usually is a sudden increase *in* the size and hormone production of the thyroid, indeed "puberty goiters" may develop. In OLD AGE the thyroid involutes and shows histologic characteristics of decreased functional activity.

Sex. — In most animal species, including man, the thyroid tends to be larger *in the* female than in the male.

but the sex difference is not very striking.

Sexual Cycle. — A transitory enlargement of the thyroid occurs in many animal species at or about the time of estrus. This is particularly obvious in monoestrous species, such as some types of birds, in which the thyroid is markedly enlarged during the breeding season.

In women, there is sometimes a transitory enlargement of the gland at, or about, the time of menstruation.

Pregnancy. — During gestation, the thyroid shows considerable enlargement in various animal species. In women this may be accompanied by signs of mild hyperthyroidism. The stimulation of the thyroid during pregnancy is probably due to excessive production of thyrotrophin although this has not yet been definitely proven.

Metamorphosis. — Since the metamorphosis of amphibia is dependent upon the thyroid hormone, it is hardly surprising that the gland enlarges and shows signs of increased activity at the time of transformation from the larval to the adult form.

Moulting. — The thyroid proliferates at the time of moulting, that is, the shedding of plumage in birds or the exchange of the cutis in reptiles. This probably is of functional importance since thyroid hormone can induce moulting, even out of season.

Hibernation. — During hibernation, in such animals as the hamster, squirrel, etc., the thyroid undergoes profound atrophy, comparable in severity to that caused by hypophysectomy The resulting decrease in thyroid-hormone production is essential for winter-sleep, since thyroid hormone administration awakens animals from this condition.

Temperature Changes. — Exposure to cold causes a compensatory increase in thyrotrophin production which leads to marked morphologic and functional stimulation of the thyroid. Thus, rats kept at a temperature of −1°C., for about one month, usually have greatly enlarged thyroids which exhibit histologic signs of hyperplasia, similar to those produced by thyrotrophin injection. It is believed that the resulting increase in thyroid-hormone production plays an important rôle in the phenomenon of adaptation to cold, since it facilitates compensatory heat production through an increase in tissue metabolism.

Drugs. — The thyroid changes induced by variations of the IODINE content of the diet, as well as the goiters which can be produced experimentally by CYANIDE administration, have been reviewed above (See: Diet.) It is believed that these "anti-thyroid drugs" act mainly by causing a relative iodine deficiency (inhibition of intestinal absorption, impairment of selective retention by thyroid, etc.). Hence, simultaneous administration of iodine with cyanides prevents the goitrogenic effect of the latter, but if iodine is given after a cyanide-goiter is formed, severe hyperthyroidism results, presumably due to precipitous hormone formation by the iodine-hungry hyperplastic gland.

The thyroid-stimulating effect of THIOUREA (see also p. 764) and its derivatives have assumed special practical importance, since these compounds are used in the treatment of hyperthyroidism Probably thioureas impede the enzymatic coupling of inorganic iodine with tyrosine. They do not appear to impede the utilization of iodine previously present in the gland, or the discharge of already-formed thyroid hormone from the gland into the blood It is understandable, therefore, that the action of the thioureas is delayed in individuals who have been pretreated with iodine and have adequate organic iodine stores. The thioureas also act through the anterior-pitui-

tary, which responds by increased thyrotrophin production when the thyroid-hormone formation is impeded as a result of the drug's action. Yet, thioureas also appear to augment the action of injected thyrotrophin.

The goitrogenic action of SULFONAMIDES and related compounds is similar to that of the thioureas.

Rays. — X-RAYS or RADIUM emanation cause some destruction of thyroid tissue but this gland is comparatively resistant to their action.

VISIBLE and ULTRAVIOLET LIGHT stimulate the thyroid, especially in species (*e.g.*, *hibernating animals*, birds) which have a definite seasonal sex-cycle

DISEASES OF THE THYROID

MALFORMATIONS

Complete APLASIA of the thyroid is extremely rare. It will be discussed in connection with the clinical syndrome of cretinism, to which it gives rise.

It is doubtful whether primary HYPOPLASIA exists since we have no means of diagnosing it. In the event of an insufficiently developed but otherwise normal thyroid, inadequate thyrotrophin production by the anterior-lobe is the most probable pathogenic factor With the thyroid (as with the male and female *gonads or the adrenal cortex*), it must be kept in mind that the postnatal condition of the gland is almost exclusively under the influence of a self-regulating pituitary control. Even if these organs were insufficiently developed during embryonic life, their normal adult size could be attained under the influence of a compensatory excess in trophic hormone production, if the *existing tissue is normal and receptive* to hormonal stimulation For the same reason, PARTIAL APLASIA is of little clinical significance since in patients in whom one lobe, or part of a lobe, fails to develop, the remaining glandular tissue undergoes compensatory hypertrophy and fully compensates for the loss.

The HYPERPLASIAS of the thyroid are discussed under Simple Goiter, Hyperthyroidism and Hypothyroidism, depending upon whether they are associated with no endocrine disturbance, hormone deficiency or excess hormone production. As far as is known all types of thyroid hyperplasia result from excessive thyrotrophin production.

ACCESSORY THYROIDS may be found at any point between the foramen cecum at the root of the tongue (whence the thyroid primordium originated) and the normal location of the postnatal gland. These accessory thyroids may take the form of a partially or completely separated pyramidal lobe, a thyroglossus cyst or a lingual goiter

The so-called "lateral aberrant thyroids" are found at some distance from the midline, outside of the normal pathway followed by the thyroid primordium during embryonic development. They are claimed to exhibit a great tendency to undergo malignant transformation, but many allegedly pertinent cases represent lymph-node metastases of thyroid carcinomas, rather than true developmental anomalies. It must be kept in mind that even seemingly benign thyroid tissue can give rise to metastases (see : page 771) hence it is not incompatible with our view that carcinomas of "lateral aberrant" glands are sometimes found in the absence of detectable malignancy in the thyroid itself. It is improbable that the "lateral aberrant thyroids" are derivatives of the lateral thyroid primordia since the latter do not appear

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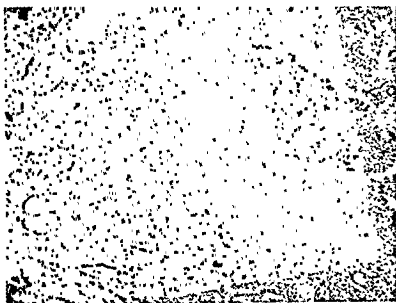
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he so-called THYROIDITIS OF CHAG-
which is often associated with hypo-
roidism, is particularly frequent in
ain regions of Brazil It had been
sidered to be a specific thyroid in-
mation due to infection with Try-
osoma cruzi. However, the rela-
ship between the trypanosoma and
myxedema is coincidental, trypan-
miasis merely happens to be com-
n in a region in which goiter is also
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special form of chronic thyroid in-
mation is the so-called "WOODY
ROIDITIS" OR RIEDEL'S DISEASE As
name implies, this is characterized
a particularly hard, ligneous indura-
of the thyroid, due to excessive
liferation of fibrous tissue which
ds to replace the active parenchyme
he gland There is little lymphocyt-
infiltration The condition appears to arise from the capsule and to spread along the blood vessels. It may be diffuse or limited to a certain area of the gland

This lesion has an approximately equal incidence in men and women; it often occurs before 40 years of age When the process involves the major part of the gland, it causes signs of hypothyroidism. In the event of excessive connective tissue proliferation, it may also lead to compression of the esophagus, trachea and adjacent blood vessels or nerves In such instances, the clinical differentiation from indurating thyroid cancer may be difficult.

The etiology of the condition is unknown

Therapeutic efforts are rather unsuccessful, the operative risk is comparatively high and recurrences are common. In the event of intense tracheal compression by the fibrous tissue, tracheotomy may be necessary to facilitate respiration Thyroid administration should only be instituted if manifestations of hypothyroidism develop

to be important in the formation of the human thyroid.

The INTRATHORACIC THYROID is of special clinical importance because, hidden from direct inspection, it may readily be overlooked. It tends to cause mechanical difficulties due to mediastinal compression; for instance cyanosis, venous stasis with the development of a collateral circulation, deformation of the trachea, esophagus or even the sternum, dyspnea and dysphagia. If an intrathoracic thyroid compresses the recurrent laryngeal nerve, dysphonia and sometimes alarming respiratory difficulties may ensue.

The intrathoracic thyroid results either from an exaggerated caudad migration of an aberrant thyroid nodule, or — and this is much more frequent — it is merely due to the downward growth of a goiter which originated in an orthotopic thyroid. In this latter case it does not represent a true malformation.

The STRUMA OVARII is a rare and singular type of ectopic thyroid; it has been discussed in conjunction with the Ovarian Tumors. (See p. 451.)

The DIAGNOSIS of all these developmental anomalies of the thyroid is based mainly upon the presence of local physical signs detectable by palpation or X-rays. The administration of radioactive-iodine is sometimes also a useful diagnostic aid. This element, like ordinary iodine, is selectively stored in thyroid tissue where its presence is readily detectable in vivo with the Geiger counter

The THERAPY of ectopic thyroid tissue in any location is always surgical. In many instances, small ectopic thyroids cause no inconvenience, but it must be kept in mind, that they are rather subject to abnormal development (e g., neoplastic transformation, with or without a resulting hyperthyroidism) and that they may cause serious mechanical difficulties in certain locations.

DEGENERATIONS

Amyloid goiter. — Extensive amyloidosis of the thyroid is rare and usually the result of chronic pulmonary tuberculosis, purulent bronchitis or neoplastic diseases, which produce general amyloidosis in other organs as well. There may be an enlargement of the thyroid but evidences of hypothyroidism do not occur. The condition is of no special clinical interest, except for its possible confusion with thyroid cancer.

INFLAMMATIONS

Acute thyroiditis. — Acute thyroiditis may develop in the course of numerous systemic infections. It has been seen after scarlet fever, typhoid fever, dental infections, tonsillitis and even rheumatic fever. Primary acute thyroiditis, without any inflammatory lesions elsewhere, is extremely rare.

The inflammatory process in the thyroid may be localized or it may affect the whole gland, causing local swelling, pain and hyperemia. It is often accompanied by fever and polynuclear leucocytosis, especially if frank suppuration ensues It rarely leads to severe hypothyroidism, except in the event of repeated inflammatory attacks which gradually destroy most of the glandular tissue.

The treatment should be primarily designed to combat the causative infection (sulfa-drugs, penicillin, etc) In the event of considerable local disturbance, analgesics and topical application of cold or heat may become necessary. A sudden increase in size is often accompanied by compression of the trachea and fluctuation of the mass. In such cases suppuration must be suspected and exploratory puncture with subsequent drainage of the abscess is to be recommended.

Chronic thyroiditis. — Chronic thyroiditis may result from SYPHILIS, TUBERCULOSIS, ACTINOMYCOSIS, ECCHINOCOCCUS, etc. All these inflammations

GOITER IN GENERAL

In its original sense, the word goiter is synonymous with thyroid enlargement. It is uncommon, however, to designate as goiters, enlargements due to proliferation of non-thyroid tissue (e.g., dermoids, echinococcus cysts or inflammatory lesions).

From the PATHOLOGIST'S VIEWPOINT, the true goiters (those which consist of thyroid parenchyme) should be classed as hyperplasias, adenomas or carcinomas; yet in this book the hyperplasias and adenomas will be treated in the sections on Simple Goiter, Hyperthyroidism or Hypothyroidism, depending upon the accompanying hormonal disturbance, if any. The carcinomas are discussed in the chapter on the Tumors of the Thyroid, since their chief clinical importance lies in their blastomatous growth.

The AMERICAN ASSOCIATION FOR THE STUDY OF GOITER has adopted the following terminology and classification:

(1) *Nontoxic goiter*:
   (a) Diffuse (endemic and adolescent).
   (b) Nodular (adenomatous or colloid).
(2) *Toxic goiter*:
   (a) Diffuse (Graves' disease, primary hyperthyroidism).
   (b) Nodular (toxic adenoma, secondary hyperthyroidism).
(3) *Malignant goiter*.
(4) *Inflammatory disease*.

From the ENDOCRINOLOGIST'S VIEWPOINT, the greatest emphasis must be laid upon the functional (endocrine) condition of the thyroid. Thus we distinguish the following types

(1) *Simple goiters* which lead to no endocrine symptoms

(2) *Hypothyroid goiters* which lead to a deficiency in the endocrine secretion of the gland

(3) *Hyperthyroid goiters* which lead to an excess of thyroid secretion

It will be noted that the first group in this classification comprises the functionally asymptomatic goiter in which the thyroid enlargement causes no abnormality in the hormone production of the gland. In this book, for the sake of simplicity, goiters resulting in hypothyroidism and hyperthyroidism (groups 2 and 3 respectively) will be treated together with those types of glandular hypo- and hyperfunction which are not accompanied by an increase in its size.

SIMPLE GOITER

DEFINITION

The terms "simple goiter" or "endemic goiter" have often been used to designate hormonally-asymptomatic thyroid enlargements It will be kept in mind, however, that originally asymptomatic simple goiters may eventually destroy enough thyroid tissue to cause hypothyroidism or they may become hyperactive and cause hyperthyroidism It is also noteworthy that simple goiters are not always endemic, they sometimes occur sporadically in otherwise goiter-free regions. All these facts indicate that it is not possible to draw a sharp line of demarcation between the "simple" goiters on the one side and those causing hypo- or hyperthyroidism on the other.

CLASSIFICATION

The strict subdivision of simple goiters into the DIFFUSE and NODULAR types is perhaps somewhat artificial since many transitional forms occur between these two extremes. Yet it is noteworthy that in some cases, the entire thyroid is uniformly enlarged, while in



Lymphatic struma. Several germinal centers in the lymphatic tissue found within this thyroid. The central part of the field consists of thyroid follicles.

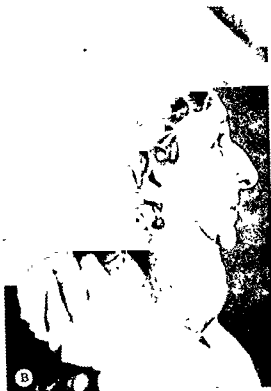
The so-called "STRUMA LYMPHOMATOSA" OR HASHIMOTO'S DISEASE was first described in 1912. It leads to a rather diffuse but moderate enlargement of the thyroid which develops more slowly than Riedel's thyroiditis, but eventually progresses towards severe hypothyroidism by gradual destruction of the gland. The thyroid is less hard and more resilient than in Riedel's disease. Unlike the latter, struma lymphomatosa occurs much more commonly in women than in men and is rare before 40 years of age

Histologically, the gland shows diffuse infiltration with lymphocytes; this causes widespread destruction of the thyroid parenchyme followed by fibrosis. As in the so-called lymphadenoid goiter, germinal centers are quite common and many investigators believe that the latter is merely a modification of Hashimoto's disease. Sclerosis, lymphocytic infiltration and compression as well as destruction of thyroid acini, with the formation of solid large-cellular nodules are common characteristics of various types of: chronic thyroiditis, so-called thyroid-hypoplasia, "primary atrophy," Riedel's and Hashimoto's disease; this suggests close, essential interrelations between these maladies conducive to thyroid involution. The resemblance of the solid large-cellular foci found in these conditions resemble those of the Hürthle cell tumors. (See : Tumors of the Thyroid, p. 772.)

The etiology of struma lymphomatosa is unknown but its histologic characteristics are not typical of inflammatory lesions. It is listed in this section merely because it appears more closely related to the inflammatory granulomas than to the other diseases of the thyroid

Surgical therapy is rarely employed but some workers recommend an extensive subtotal thyroidectomy. It should be kept in mind that the lymphatic elements in this type of goiter are very sensitive to X-rays, and at least temporarily satisfactory results may be obtained by irradiation. Of course, in the event of hypothyroidism, thyroid therapy is indicated.





Endemic goiter. — A. and B. Marked unilateral enlargement of the thyroid with radiologically demonstrable calcifications and deviation of the trachea No manifest hormonal derangement was present (Courtesy of Dr E B del Castillo)

ing mass Among the secondary changes which may affect the goitrous thyroid, the most common are liquefaction necrosis (which leads to cyst formation), calcification and hemorrhage

PATHOGENESIS

A number of theories have been proposed to explain the origin of simple goiter. Among these the INFECTIOUS, NUTRITIONAL and TOXIC theories were especially popular. It is now generally recognized, however, that IODINE DEFICIENCY is the fundamental cause of simple goiter This iodine deficiency may eventually cause a disturbance in thyroid-hormone production with the clinical syndrome of hypothyroidism. evidence supporting the iodine deficiency theory will be discussed in detail in the chapter on Hypothyroidism

INCIDENCE

The incidence of goiter has shown a very rapid decrease as a result of iodine prophylaxis. Women are much more frequently affected than men; in the case of sporadic goiter, the proportion is 10 to 1 Simple goiter may be congenital and cause death soon after birth, by pressure upon the trachea.

CLINICAL COURSE

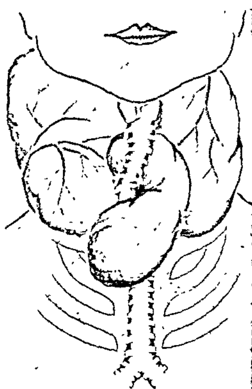
Usually, simple goiter gives no serious cause for complaint apart from its esthetic aspects. In women, a swelling of such goiters is frequently noted at puberty, during menstruation and pregnancy, while after the menopause, they tend to involute. Spontaneous disappearance of smooth (but not of nodular) puberty goiters is likewise common

others one or more circumscribed nodules, the so-called "non-toxic adenomas" are found

PATHOLOGIC ANATOMY

In DIFFUSE GOITERS, the enlargement may be due to an increase in the number of thyroid follicles, in which case we speak of *parenchymatous goiter*. Alternatively, the size of the individual follicles may be augmented so as to form definite cysts, filled with colloid. In this event, the lesion is designated as *colloid goiter*. The term *fibrous goiter* is employed when sclerosis of the connective tissue predominates.

The NODULAR GOITER is characterized by the formation of one or more individual, circumscribed, thyroid adenomas. Here, again, the nodules may be *parenchymatous* or *colloid*, depending upon whether they consist of many small or of comparatively few large follicles. These adenomas are frequently surrounded by a definite connective tissue capsule; this facilitates their surgical enucleation



Complex nodular goiter. Schematic drawing made at operation. Note intrathoracic and retrotracheal processes as well as abundant blood supply of this complex goiter.
(Courtesy of Dr A Pinto Viegas)

Both the diffuse and the nodular asymptomatic goiter can be small, but they can also assume considerable proportions and hang down in front of the sternum in the form of a huge, disfigur-



Microfollicular goiter. The tumor consists of small, colloid-filled follicles and undifferentiated regions in which follicle formation is indistinct It led to no hormonal disturbances
(Courtesy of Dr P Masson)



Substernal goiter. Note markedly dilated veins on anterior surface of sternum.
(After W M Yater "Fundamentals of Internal Medicine" Appleton Century Publ 1944)

given excellent results, especially in regions where simple goiter had been endemic

Iodine is also a curative measure in many cases of fully developed simple goiter. It can be administered as the U.S P tincture of iodine, in quantities of about 20-50 drops, divided into four or five daily doses which may be taken in milk. Alternatively, Lugol's solution (iodine, 1 gm.; KI, 2 gm , water, 30 cc) may be prescribed in the same daily doses Some physicians prescribe 10-15 mg. of KI or NaI daily during alternate months. A maximum reduction in goiter-size is usually noted after 6-12 months With non-toxic, nodular goiters, the danger of producing thyrotoxicosis by iodine treatment is real but not as serious as has been believed, especially if the dosage is well controlled. Old, cystic and fibrous goiters are singularly resistant to iodine therapy.

Desiccated thyroid may be given in the form of the U S.P. preparation in average daily doses of 30-60 mg. (0.5 to 1 0 grain); it produces a compensa-

Thus the usual course of asymptomatic goiter is uneventful but important complications can arise.

COMPLICATIONS

The complications which may influence the clinical course of simple goiter are the following :

(1) Endocrinologic complications.

(2) Mechanical and infectious complications.

(3) Malignant transformation.

As regards the ENDOCRINOLOGIC COMPLICATIONS, it must be kept in mind that an originally asymptomatic thyroid enlargement may eventually so upset the function of the gland as to cause hypothyroidism. Such a course is more common with endemic than with sporadic simple goiter. Secondary hyperthyroidism is due to the "basedowification" of asymptomatic goiters. (See: p. 743 and "Jod-Basedow," p. 723.)

MECHANICAL COMPLICATIONS are due to compression of adjacent organs by a rapidly growing thyroid tumor. These are disturbances of swallowing, hoarseness, dyspnea and cardiac failure. The so-called "goiter heart" is largely due to mechanical causes and not to hyperthyroidism Finally, disturbances in the function of the recurrent laryngeal nerves may occur, due to compression: if bilateral, this may cause aphonia.

Incidental INFECTIONS may lead to inflammation of the goiter, that is, strumitis. In this event, as in the case of intraparenchymatous hemorrhage, the enlargement of the goiter may be rapid and consequently very acute mechanical complications tend to develop.

The MALIGNANT TRANSFORMATION of simple goiters results in the development of thyroid cancers, these will be discussed separately (see : p 771)

DIAGNOSIS

The diagnosis of simple goiters is rarely a serious problem unless the enlargement occurs in ectopic thyroid tissue. A suspicious tumor in the thyroid region must first be identified as belonging to the thyroid gland and secondly, as being goitrous in nature.

From the differential point of view, prethyroid cysts, prethyroid lipomas, enlarged lymph-nodes and aneurysms of the aortic arch which protrude above the sternum, have occasionally caused difficulties. If the examiner remembers these possible causes of error, the features characteristic of each of these lesions usually permit a correct diagnosis.

Inflammations of the thyroid tend to occur in conjunction with some acute (e.g., typhoid, septicemia), or chronic (e.g., tuberculosis, syphilis) systemic infectious diseases. Echinococcus cysts are particularly difficult to diagnose, without knowledge of antecedents, but because of their rarity they are less important.

In individuals over 50 years, thyroid cancer should always be suspected but only histologic examination can ascertain the diagnosis with absolute finality.

PROGNOSIS

As stated above, the course of simple goiter is usually uneventful unless one of the above-mentioned complications arises. The thyroid enlargements of puberty and pregnancy usually undergo spontaneous regression. On the other hand, a well developed and persistent simple goiter may not respond to the usual therapeutic measures (see below) and it is much easier to prevent this condition by prophylactic iodine administration than it is to cure it.

THERAPY

The best procedure to combat the development of simple goiter is IODINE prophylaxis (e.g., in the form of NaCl containing about 0 01% KI, to be used as table salt and for consumption by domestic animals). This method has

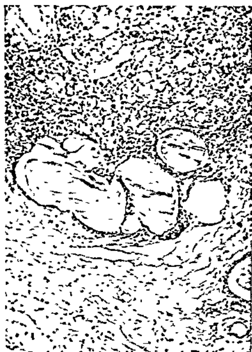
common cause of clinical hypothyroidism. It may be diffuse or nodular and essentially resembles simple goiter in its histologic aspects. (See: Simple Goiter, p. 716.)

(2) "PRIMARY ATROPHY" is a process which leads to infiltration of the thyroid by connective tissue and lymphocytes. In extreme cases, only occasional remnants of follicles are found in the dense stroma. The etiology of this condition is unknown. In some instances, a previous inflammatory process may be suspected.

(3) CHRONIC THYROIDITIS may destroy so much of the gland that functional insufficiency ensues. The morphologic appearance of the thyroid will then be characterized by the features typical of the causative inflammatory reaction (e g, syphilis, tuberculosis)

(4) SECONDARY ATROPHY DUE TO PITUITARY FAILURE is due to destruction or hypofunction of the anterior-hypophysis, it is comparable to that seen in hypophysectomized animals. The thyroid follicles are small and contain comparatively little colloid; the follicles are lined by atrophic cells.

(5) POLYGLANDULAR INSUFFICIENCY may so affect the thyroid as to cause signs of functional insufficiency, but it is very probable that most of the purportedly relevant cases, actually represent pituitary insufficiency syndromes It is noteworthy that, under normal conditions, severe pituitary failure rarely elicits the typical picture of hypothyroidism, although the metabolism is greatly depressed and the thyroid shows the histologic picture of pronounced involution Perhaps the simultaneous elimination of other metabolic functions is responsible for the fact that the hypopituitary patient (especially in the younger age groups) does comparatively well in spite of thyroid deficiency It is probable furthermore that some thyroid function persists even after complete destruction of the anterior-lobe



Thyroid in Myxedema. — Most of the thyroid consisted of proliferating connective tissue with lymphocytic infiltrations There were only few islets of atrophic thyroid follicles such as that shown in this photograph (Courtesy of Dr T Waugh)



Thyroid in myxedema. Almost complete replacement of the thyroid by connective tissue Here the remaining follicles consist of large cells and are surrounded by numerous lymphocytes (Courtesy of Dr W Boyd)

tory atrophy which may result in the complete disappearance of a simple goiter. To avoid the possibility of severe overdosage, this therapy should not be used unless the patient can remain under observation. It will also be kept in mind that compensatory atrophy of the thyroid rarely occurs in patients with simple goiter unless the dosage is sufficiently high to cause at least a mild degree of hyperthyroidism

In many instances neither iodine nor thyroid extract are effective and then X-RAY treatment or SURGICAL REMOVAL of the excess thyroid-tissue may be attempted. The latter is particularly advisable if there is a comparatively circumscribed nodule which can readily be enucleated. If there are many nodules or if the enlargement is diffuse and removal would require extensive interventions, the advisability of an operation is doubtful. Then, only the suspicion of malignancy, mechanical complications, beginning thyroid dysfunction or the patient's severe resentment of the cosmetic effect of the tumor, are valid grounds for removal.

HYPOTHYROIDISM

(SYNONYMS: Hypothyroidism in newborn: cretinism; in adult: Gull's disease, Myxedema)

DEFINITION

Hypothyroidism is a condition in which the hormone production of the thyroid is sufficiently diminished to cause detectable deficiency manifestations

Depending upon the age at the time of onset, individual susceptibility, and the degree of insufficiency, hypothyroidism manifests itself in various forms *but for the sake of simplicity, these will* be discussed conjointly

CLASSIFICATION

The clinical types of hypothyroidism may be classified according to various points of view.

According to the AGE OF ONSET, we may distinguish between

(1) *Cretinism* (in which hypothyroidism existed from birth)

(2) *Childhood myxedema*

(3) *Adult myxedema* (Gull's disease).

This classification is justified because the severity of the manifestations is inversely proportional to the age of the patient at the time hypothyroidism makes its appearance.

According to the INTENSITY OF THE INSUFFICIENCY we may distinguish:

(1) *Complete athyroidism.*

(2) *Severe hypothyroidism.*

(3) *Moderate hypothyroidism.*

According to ETIOLOGY, we distinguish between:

(1) *Hypothyroidism due to iodine deficiency.*

(2) *Hypothyroidism due to operative removal of the thyroid* (postoperative myxedema).

(3) *Hypothyroidism due to X-ray destruction of the thyroid.*

(4) *Hypothyroidism due to destruction of the thyroid by inflammatory or neoplastic diseases.*

Finally, according to GEOGRAPHIC DISTRIBUTION, we distinguish:

(1) *Endemic hypothyroidism.*

(2) *Sporadic hypothyroidism.*

It is obvious that all these classifications overlap inasmuch as any one case may be severe or mild, endemic or sporadic and may be elicited by any of the various possible etiologic factors irrespective of the age at which it develops

PATHOLOGIC ANATOMY

Hypothyroidism may be produced by a variety of thyroid lesions:

(1) IODINE DEFICIENCY GOITER, usually of the endemic type, is the most

PATHOGENESIS

Hypothyroidism is invariably due to a physical or physiologic interference with thyroid function. Among the physical reasons which may impede thyroid-hormone production, surgical or X-ray destruction of the gland, *invasion* by neoplasms, "primary atrophy," secondary atrophy due to pituitary failure, chronic thyroiditis and primary aplasia have already been mentioned.

The most frequent cause of hypothyroidism is relative or absolute iodine deficiency. As shown by *Marine*, goiter (which often leads to hypothyroidism) may result from RELATIVE IODINE DEFICIENCY, due to an increased need of the body for thyroid hormone and iodine. Puberty, pregnancy, the menopause, certain infections and intoxications, exposure to cold, excess of certain dietary substances (e.g., certain vegetables, fats, proteins, calcium, foods which produce cyanides or prevent iodine absorption in the intestine), and inadequate oxygen supply to the tissues (e.g., anemias, life at high altitudes) are all factors which increase the thyroid hormone requirement of the organism.

As stated above, sea water is one of the main sources of iodine; the inhabitants of mountainous regions, at a great distance from the sea are especially prone to develop goiters, because their food is poor in iodine, and at the same time, the *supply of oxygen* is low at the high altitudes in which they live. It is for this reason that endemic goiter with hypothyroidism is particularly frequent in Switzerland, Slovakia, Tyrol, the interior of Brazil, the Andes, the United Provinces of India, etc.

Calcium interferes with the absorption of iodine, hence, the frequency of hypothyroid goiters, for instance among the Cachins of North Burma, is readily understandable since they not only live on an iodine-poor diet but drink water rich in calcium, and in addition are accustomed to eating calcium carbonate, as such.

Inability to absorb iodine from the intestine, *vitamin-A deficiency, "goitrogenic" food* and micro-organisms have all been considered as factors which may deprive the body of an adequate iodine intake and hence cause goiters due to relative iodine deficiency, even if this element is present in the food in normally sufficient quantities.

In other instances, the iodine intake is insufficient because of a regional poverty in iodine of the soil and water, as well as of the meat and milk of domestic animals and plants which are used for food.

Since each molecule of thyroxine contains four atoms of iodine, it is obvious that the normal elaboration of thyroid hormone is impossible if there is such an ABSOLUTE IODINE DEFICIENCY. In this case the resulting thyroid hormone deficiency stimulates the thyrotrophin production of the anterior-lobe in an effort to increase the activity of the thyroid (compensatory hypertrophy). Under the influence of this thyrotrophin excess, the gland produces large amounts of "low grade" colloid, which is not suitable for use by the body and is merely accumulated in the thyroid follicles. If small doses of iodine are administered at this time, the condition may be cured, but under the influence of ill-advised treatment with excessive doses, a "Jod-Basedow," or 'Iodine-Graves' disease" may be produced because excessive amounts of incompletely iodinized thyroid hormone precursors are turned into active thyroid-hormone and released into the circulation.

This interpretation receives further support from the observation that thyroid substance or thyroxine causes compensatory atrophy even of the normal thyroid, mainly because they depress the thyrotrophin production of the hypophysis. It is understandable, there-

(6) DESTRUCTION BY NEOPLASMS (e.g., carcinomas, teratoids) may also cause thyroid insufficiency. In such cases the thyroid merely shows compression-atrophy and replacement of the glandular parenchyme by the invading neoplasm.

(7) PRIMARY APLASIA of the gland is exceedingly rare. Even in the few cases in which no trace of a thyroid was detectable at birth, it is possible that the gland was secondarily destroyed by a pathologic process during embryonic life. There is no reason to doubt, however, that the embryonic primordium of the thyroid may fail to develop.

INCIDENCE

Congenital thyroid insufficiency is rare but other types of hypothyroidism are not and it has been estimated that about 1 of every 1,500 hospital admissions is a case of myxedema The previously very common endemic goiter, with subsequent myxedema, has almost completely disappeared as a result of iodine prophylaxis, while improvement in surgical technic greatly reduced the incidence of postoperative myxedema.

The incidence of adult myxedema in the female SEX is approximately five times as high as in the male In nongoitrous regions this ratio may even be higher (9:1).

The PREGNANCY incidence in hypothyroidism is low, partly because fertility is impaired as a result of thyroid deficiency and, I should think, partly because the women affected are singularly devoid of sex appeal.

Myxedema may develop at any AGE Congenital primary aplasia of the thyroid causes the most pronounced type of hypothyroidism, usually accompanied by dwarfism and cretinism or even complete idiocy Sporadic goiter is rarely seen before puberty but at this period many girls develop a thyroid enlargement, which is usually asymptomatic, although it may be accompanied by such signs as acrocyanosis and great sensitivity to cold; this has sometimes been interpreted as a latent type of hypothyroidism. In any case, these goiters usually disappear after puberty. Adult myxedema is most frequent between 30-60 years of age.

It had previously been thought that HEREDITY has a great deal to do with the development of myxedema because several cases tended to occur in the same family. It must be kept in mind, however, that iodine deficiency is the most common cause of myxedema and since members of a family usually eat the same type of diet, the familial occurrence of the disease is no proof of hereditary transmission. Endemic cretinism is found among the children of goitrous mothers, but here prenatal iodine deficiency, rather than a genetic factor, appears to be the cause.

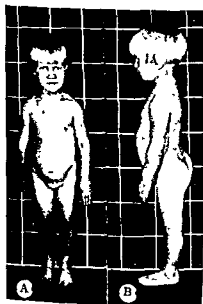
Apparently all races are subject to hypothyroidism, although the Japanese are practically free of endemic goiter because their iodine consumption is about twice that of most other nations

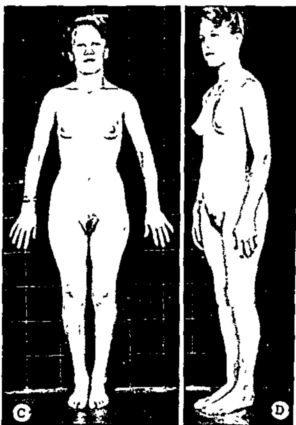
The GEOGRAPHIC DISTRIBUTION of endemic hypothyroidism was the subject of extensive studies before the rôle of iodine deficiency was understood. However, a survey of the pertinent data shows that, in almost every instance, lack of iodine accounts for the endemic development of the disease Sea water contains about 0 02 mg. of iodine per liter, hence, along seashores, where marine iodine is plentiful, endemic goiter and the resultant hypothyroidism are comparatively rare. Conversely, in the central parts of continents and especially in mountainous countries, where dietary iodine is comparatively scarce, hypothyroid goiters are common unless iodine prophylaxis is used (See: Pathogenesis, p 723.)





(Courtesy of Dr J.-I. Lobo.)





Hypothyroid cretinism. — A and B [illegible]

[illegible] bone growth and mental development very obvious. — C and D. Same patient at 18 years of age. Continuous treatment with 1-2 grains of thyroid/day resulted in marked bone-growth and mental development. She was able to attend high school and her menses were normal.

(Courtesy of Dr. E.-K. Shelton.)

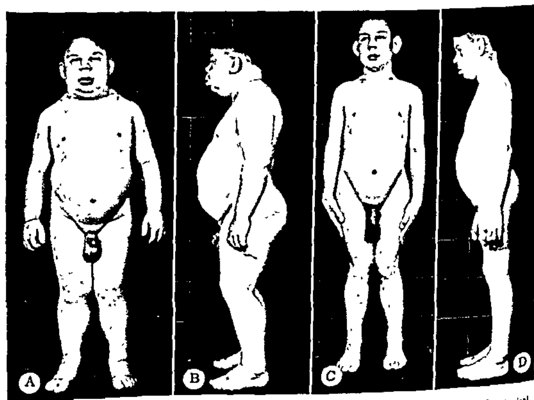
fore, that thyroid hormone tends to cause involution of hypothyroid goiters with atrophy of the follicular epithelium and disappearance of the colloid.

CLINICAL COURSE

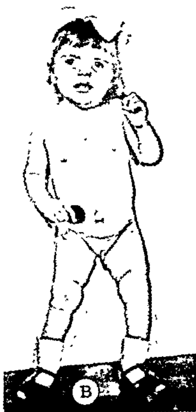
State. — The appearance of the hypothyroid patient is very characteristic, especially if the condition began at an early age, is of long standing and is caused by severe thyroid-hormone deficiency. The general appearance is similar in cretinism (with hypothyroidism since birth) and in childhood myxedema (where thyroid function was normal at birth but failed very early in life); although the manifestations of thyroid deficiency, particularly the mental retardation, are more severe in the former. The patient with congenital or childhood myxedema is dwarfed, of stocky build and usually overweight, but not markedly obese. The facial expression is very characteristic because failure of naso-orbital development causes the bridge of the nose to be flat and broad so that the eyes are set far apart. The features are coarse, the lips are thick and, in severe cases, the protruding tongue imparts a definitely imbecile expression to the patient. The hands are spade-like and stubby.

In adult myxedema, growth in length is normal, since bone development has been completed at the time of onset. The condition is mainly characterized by the myxedematous infiltration of the skin which causes puffiness of the face, especially around the eyelids, swelling of the tongue, loss of hair and slowing of both mental and physical reactions.

All types of hypothyroid patients have a LOW RESISTANCE TO INFECTIONS, COLD AND OTHER DAMAGING AGENTS.

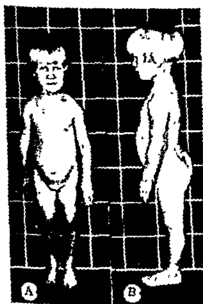


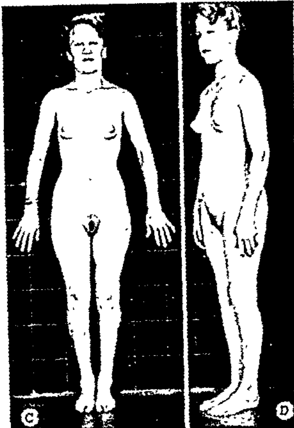




Hypothyroid *cretinism.* — A. Three-year-old hypothyroid cretin, showing typical *facies, protruding* thick tongue, *saddle nose* and thick skin prior to therapy. — B. Same child following fourteen months of thyroid treatment.

(Courtesy of Dr. J.-I. Lobo.)





school and her menses were normal

(Courtesy of Dr. E. K. Shelton.)





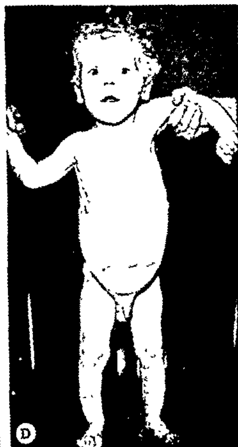






Hypothyroid cretin. Child suffered from severe hypothyroid cretinism and megacolon. The picture series shows progressive improvement under the influence of continuous thyroid therapy — A. Age 3½ years. Note cretinoid facies, prior to therapy. (Cont'd on p. 727)





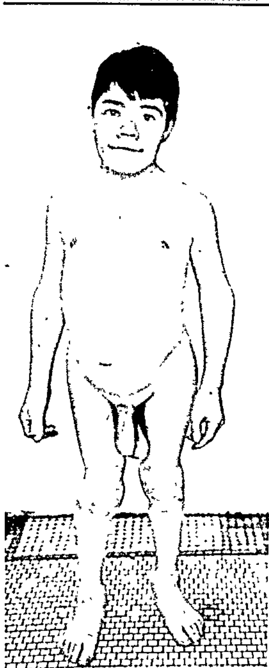




— B. Age 3½ years Note cretinoid facies protruding tongue bulging abdomen (megacolon) wrinkled skin and deformed bones — C. Age 3 years and 8 months Thyroid therapy begun — D. Age 3 years and 11 months — E Age 4 years and 3 months — F. Age 4½ years — G. Age 5 years — H. Age 5½ years — I. Age 7 years (Courtesy of Dr E.-P McCullagh)

Hypothyroid cretinism. — A and — B Typical aspect of hypothyroid cretinism in a Negro girl from a region of Brazil where goiter is endemic
(Courtesy of Dr A Pinto Viegas)

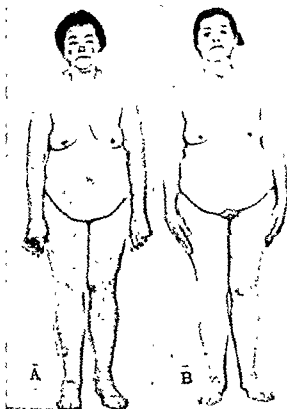




Hypothyroid cretinism. Age 28 years dwarfism and cretinism, (mental age between 4 and 5 years I Q approximately 35) B M R —28% features somewhat mongoloid skin dry and firmly adherent to subcutaneous tissue hair coarse axillary hair absent pubic and facial hair scanty, external genitalia of adult size thyroid not palpable, abdomen protruding Patient improved considerably under the influence of thyroid treatment
(Courtesy of Dr E-H Mason)



Hypothyro[illegible] [illegible] the ext[illegible] (about 55 x 30 mm each) Mental [illegible] ordinarily large [illegible] tion was very obvious
(Courtesy of Dr A Pinto Viegas)



Adult myxedema — A. Woman age 54 years Onset, 7 years before Previously diagnosed but now untreated for 8 months Shows puffy features coarse dry hair, malar flush moderate obesity slow clumsy movements, low-pitched voice Gained 40 pounds in the last 7 years *Chief complaint generalized aches* and pains B M R —19% plasma cholesterol 378 mg %, blood pressure 185/100 carotinemia present — B Patient shown in Fig A, after 6 months of adequate treatment with desiccated thyroid substance Note loss of weight and *more alert appearance* Patient is 23 pounds lighter without dieting, skin and hair less dry, voice markedly higher in pitch Blood pressure has dropped to 130/70 B M R *has risen to —3% and plasma cholesterol* has dropped to 133 mg % Carotinemia now absent — C. Patient shown in Fig A (before treatment) Close-up of face Note *puffy appearance of face and eyelids,* with narrow palpebral apertures, edematous folds of forehead and under chin, thinning of lateral halves of eyebrows, broad nose, *malar flush, lethargic expression* — D. Patient shown in Fig B (after treatment)

(Courtesy of Drs H Lisser and R F Escamilla)



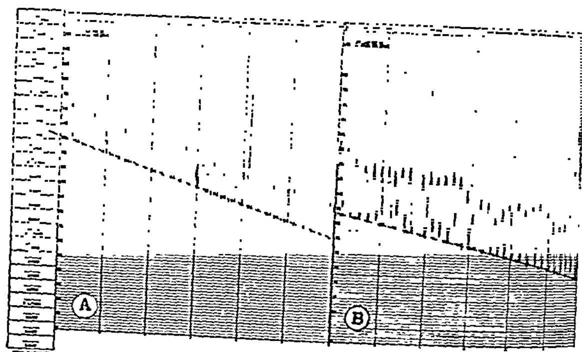


TABLE "C"

TABLE "A"

DIRECTIONS

COMPUTATIONS AND DATA

TABLE "B"

(C)

B.M.R. in hypothyroidism. — A. B M R record of a normal adult obtained with the Benedict-Roth recording metabolism apparatus, note normal frequency of respiratory movements and normal oxygen consumption B M R —6%, pulse 70 — B. Low B M R record in severe hypothyroidism Note rarity and slowness of respi[illegible] sumption B.M.R —46%, pulse 58 — C. Data us[illegible] paper used in the B M R apparatus Note chart for [illegible] normal standards with which the data are to be compa[illegible] correction for temperature and barometric pressure in the examining room (Table 'C") This sheet gives the data of the hypothyroid patients shown in figure B

(Courtesy of Royal Victoria Hospital Montreal)

Adrenaline causes glycosuria in normal individuals because it suddenly converts a large amount of hepatic glycogen into glucose. In hypothyroid patients, adrenaline glycosuria is absent or mild.

The most characteristic disturbance in LIPID METABOLISM is the increase in blood cholesterol which is frequently in the vicinity of 300 mg.% and may reach values as high as 700 mg.% (normal about 180 mg %). The total lipid content of the blood is likewise increased but, contrary to common belief, adiposity is not characteristic of hypothyroidism. Myxedematous deposits in the skin may imitate adiposity but "cachexia strumipriva" is the typical result of severe hypothyroidism although, in mild cases, a tendency towards fat deposition may be observed. B.M.R. measurements in adipose patients are not very satisfactory and many instances of obesity have erroneously been diagnosed as due to hypothyroidism because the B.M.R. values were calculated to be low. In the absence of other signs of thyroid deficiency, a low B M.R. in an adipose patient is not pathognomonic.

NITROGEN METABOLISM is also deranged in hypothyroidism. Urinary N.P.N. excretion is decreased. The *albumin* content of the blood decreases to such an extent that the albumin/globulin ratio is reversed (as in lipid nephrosis). The myxedema fluid contains about 13% *protein*. The urinary elimination of *creatine* is decreased While in normal children, on a meat-free diet, 0 6-7 8 mg creatine/Kg body weight/24 hours is excreted, in hypothyroid children, the corresponding figures range between 0 and 3 8 mg

Among the disturbances in SALT AND WATER METABOLISM, the derangement in the metabolism of *iodine* is the most important. The iodine content of the blood and thyroid is decreased. Many of the technics for the determination of iodine in biologic material are unreliable, however, and hence the results reported by various investigators are somewhat contradictory. According to the most reliable, pertinent data, in normal persons the average iodine content is about 4γ/100 cc. of whole blood and 7.1γ/100 cc. of plasma, while the corresponding figures in hypothyroid patients are much lower.

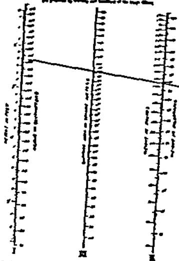
It will be recalled that the thyroid hormone is present in the albumin fraction of the blood plasma. In normal persons about 2 4-8 0γ of iodine/100 cc. of blood is present in the form of protein-iodine (presumably the hormone) while in hypothyroidism this amount falls to, or below, 2γ.

The hyperplastic, non-toxic, nodular goiter of hypothyroid patients has a great avidity for iodine. If iodine is given it is accumulated in large quantities, especially in the cells, less so in the colloid.

The metabolism of OTHER ELECTROLYTES show no significant disturbance, although, of course, the retardation of skeletal development in children results in a subnormal anabolism of calcium and phosphorus.

True EDEMA is not infrequent in hypothyroid patients but it is often masked by the myxedematous condition.

Growth and Bone Structure. — It is very characteristic of congenital and juvenile hypothyroidism that the appearance of the ossification points is delayed and the union of the junction cartilages is retarded Thus the bone-age of the patient remains far behind his actual age, a point which is of diagnostic significance In congenital hypothyroidism the closure of the anterior fontanelle is several years late (normally it occurs before the 20th



B.M.R. in hypothyroidism. — A. B M R record of a normal adult obtained with the Benedict-Roth recording metabolism apparatus, note normal frequency of respiratory movements and normal oxygen consumption B M R —6%. pulse 70. — B. Low B M R record in severe hypothyroidism Note rarity and slowness of respiratory movements and low oxygen consumption B M R. —46%. pulse 58 — C. Data usually given on the back of the recording paper used in the B M R apparatus Note chart for calculation of body surface (Table "A"), normal standards with which the data are to be compared (Table "B") and the chart permitting correction for temperature and barometric pressure in the examining room (Table "C")

This sheet gives the data of the hypothyroid patients shown in figure B

(Courtesy of Royal Victoria Hospital, Montreal.)

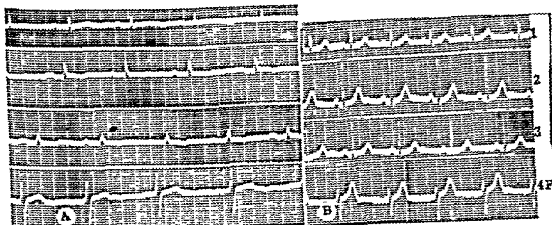
month). Periosteal apposition of bone progresses fairly normally, however, and therefore the bones are comparatively short for their width. The characteristic flattening of the bridge of the nose and stubbiness of the hands, which have already been mentioned, are likewise a consequence of abnormal ossification.

The TEETH of hypothyroid patients are very subject to caries. If the condition develops at an early age the eruption of the milk teeth is delayed and the position and shape of the teeth is very irregular.

Hypothyroidism appears to cause a specific predilection for JOINT diseases, as judged by the frequent occurrence of arthritides in hypothyroid individuals. The suggestion that osteochondritis juvenilis (Legg-Perthes' disease) and spondylitis are especially common among myxedematous individuals has not been sufficiently corroborated.

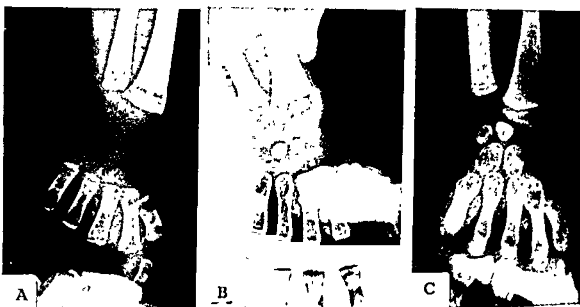
Blood Picture. — Hypochromic (sometimes hyperchromic) anemias are common among hypothyroid patients. The red corpuscle count may fall to 2-3 million and the blood hemoglobin to 50-40%. This is sometimes accompanied by leukopenia with relative lymphocytosis but none of these signs are constant.

Cardiovascular System. — As judged by X-ray and percussion, the heart of myxedematous patients is characterized by small pulsations and a generalized increase in cardiac shadow. This is often due to edema or myxedema of the heart muscle and pericardial transudates. The pulse rate is slow, about 50 or less per minute and there may be hypotension and even cardiac insufficiency. The T-waves in leads 1, 2 and 3 of the electrocardiogram may be inverted and the amplitude of the complexes is reduced. When decompensation develops pitting edema appears on the lower portions of the body and there may be pleural effusions. This so-called "myxedema heart," first described by *Zondek* in 1918, generally appears in patients around 50 years of age, although it may be seen earlier in life. Digitalis therapy is ineffective but thyroid adminis-



Electrocardiogram in myxedema. — A. 57-year-old man with untreated myxedema. Characteristic electrocardiogram with bradycardia (60/minute) but otherwise regular heart beat. Low-voltage QRS and low or negative T-wave in leads 1, 2 and 3 are considered typical. — B. Normal electrocardiogram of a 50-year-old man for comparison. (Pulse rate 75/minute).

(Courtesy Royal Victoria Hospital, Montreal.)



1.
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E

Hypothyroid cretinism. — A 3½-year-old hypothyroid cretin Hand and wrist show development normal for a newborn baby — B Same patient after 9 months of thyroid treatment Two carpal bones and distal epiphysis of radius are evident Skeletal maturity about that of a normal 2-year-old — C After 22 months of thyroid feeding the phalangeal epiphyses of 5 carpal bones and distal radius epiphysis are well-developed Skeletal maturity now corresponds to the actual age of the patient (5 years) — D E C G before thyroid therapy showing low amplitude of Q R S complexes and slight right axis deviation The upward displacement of S T segments in leads 1, 2 and 4 with flattening of the T waves are especially characteristic — E E C G after 18 months' of thyroid treatment shows conversion to normal type Note the apparent increase in the amplitude of Q R S complexes and well-demarcated T Waves (Courtesy of Dr E.-P McCullagh)

with various degrees of imbecility. In adult myxedema, the salient characteristics are: slowing of mental reactions, a slurring, defective speech, poor memory, somnolence, decrease in libido, paresthesias and a general indolence towards life. However, in some cases of adult myxedema, temporary mental depressions, schizoid or anxiety states have developed and occasionally, under the influence of thyroid therapy, a previously indolent, cretinoid patient may become highly excitable. This is especially true of congenital hypothyroid cretins in whom cerebral inhibition is subnormal so that under the influence of a stimulus, such as the thyroid hormone, the excitability of the lower nerve centers becomes excessive. For this reason, in many institutions for the insane, happy hypothyroid cretins are not given thyroid treatment which would only excite them.

The cause of the nervous manifestations is not completely understood but at least in the most severe congenital cases, myxedematous infiltration of the brain was found and this as well as a lack of brain development may be the main etiologic factors. This view is in agreement with the observation that thyroid-hormone treatment initiated in adult life, has little effect upon the mentality in congenital and juvenile hypothyroidism, although it is effective in adult myxedema.

Sense Organs. — The senses of taste and hearing are often imperfect in hypothyroidism, probably because of myxedema in the corresponding mucous membranes. The "endemic deaf-muteness," which used to be common in goiter regions, has almost vanished since the introduction of iodine prophylaxis.

Digestive System. — Hypothyroidism causes dryness of the oral and pharyngeal mucosa, often accompanied by halitosis. In congenital cases, there may be hypertrophy of the tongue due to myxedematous infiltration of its muscles. Achlorhydria interferes with gastric digestion, while torpor of the intestinal contractions result in constipation and flatulence. Salivary and intestinal secretion is inadequate; this adds to the difficulty of deglutition and digestion.

Skin. — The skin of hypothyroid patients is dry, scaly and infiltrated by the typical mucoid, egg-white-like, myxedema fluid which contains large amounts of protein. Sometimes this infiltration is patchy and imitates bulges of subcutaneous fat. True pitting edema is also quite common in hypothyroid patients because of cardiac decompensation.

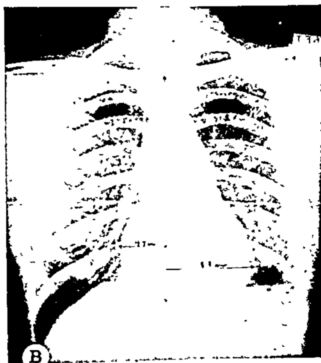
The sweat and sebaceous secretions are diminished, pubic and beard hair are scarce and there may be complete, or at least temporo-occipital, baldness. The nails are usually short, atrophic and brittle

Urinary System. — There may be some protein and a few casts in the urine and usually there is oliguria. All the symptoms readily disappear after thyroid hormone administration.

Sex Organs. — As stated above, the libido of hypothyroid patients is frequently subnormal and sometimes completely absent. Male hypothyroids are usually impotent and females may suffer either from amenorrhea or from irregular menorrhagias The vagina may be infiltrated by myxedematous tissue which impedes coitus. These disturbances do not necessarily result in absolute sterility, although they greatly diminish fertility

The hypothyroid condition which results in a child-like soma with immaturity of genital development is referred to as the BRISSAUD TYPE OF INFANTILISM.





Heart in myxedema. Man, age 33 years, with typical myxedema B M R —40%, blood cholesterol 526 mg %, typical myxedematous appearance — A. Chest X-ray before treatment showing greatly enlarged cardiac shadow — B. Practically normal cardiac shadow of the same patient following thyroid hormone treatment (Courtesy of Dr E.-H Mason)

tration causes a remarkable decrease in the cardiac X-ray shadow with restoration of normal action.

Angina pectoris and hypertension are rare; they may be improved or aggravated by thyroid therapy.

Capillaroscopic examination of the nail root capillaries often shows striking deviations from the normal (pronounced narrowness of the limbs) in myxedema; these readily disappear under the influence of thyroid treatment.

Lymphatic Organs. — The lymphatic organs do not show any characteristic changes in myxedema, although the thymus may appear to be hyperplastic, due to retarded involution.

Respiratory Organs. — The respiration of the hypothyroid patient is slow and as a result of decreased tissue oxidation, there may be cyanosis of the lips and extremities. The forced and raucous voice is so characteristic that the "myxedema voice" is considered a diagnostic sign. Sometimes so-called "pseudo-asthma" develops. It is very probable that all these manifestations are due to myxedematous infiltration of the mucosae of the respiratory passages

Muscles. — The strength of hypothyroid patients is subnormal and their muscles are flabby; this is perhaps partly due to myxedematous infiltration of the muscle tissue. Such infiltration may increase the size of the muscles and produce a "pseudo-athletic" appearance. The weakness of the muscular system is responsible for the flabbiness of the anterior abdominal wall, which often results in the formation of herniae and "pot-bellies"

Nervous System. — Mental retardation is most pronounced in congenital hypothyroidism, where it results in cretinism. Childhood myxedema causes less severe mental retardation

with various degrees of imbecility. In adult myxedema, the salient characteristics are: slowing of mental reactions, a slurring, defective speech, poor memory, somnolence, decrease in libido, paresthesias and a general indolence towards life. However, in some cases of adult myxedema, temporary mental depressions, schizoid or anxiety states have developed and occasionally, under the influence of thyroid therapy, a previously indolent, cretinoid patient may become highly excitable. This is especially true of congenital hypothyroid cretins in whom cerebral inhibition is subnormal so that under the influence of a stimulus, such as the thyroid hormone, the excitability of the lower nerve centers becomes excessive. For this reason, in many institutions for the insane, happy hypothyroid cretins are not given thyroid treatment which would only excite them.

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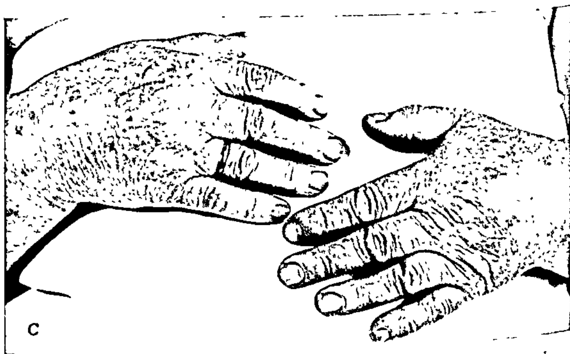
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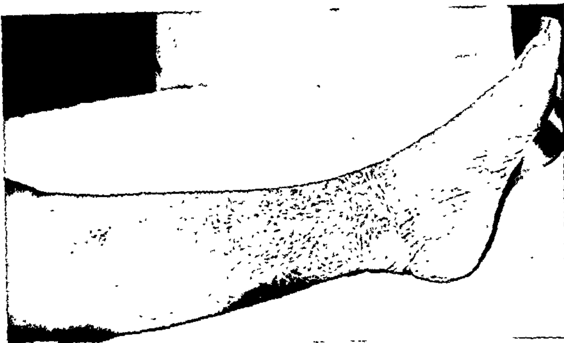
The hypothyroid condition which results in a child-like soma with immaturity of genital development is referred to as the BRISSAUD TYPE OF INFANTILISM.







Adult myxedema. — A. and B. Typical myxedematous face, thick and dry skin, brittle and dry hair — C. Dry scaly skin on hands of myxedematous woman shown in Fig. A.
(After W M Yater Fundamentals of Internal Medicine ' Appleton-Century Publ 1944)



Adult myxedema. Note drying and cracking of skin (the pigmentation is incidental)
(After W M Yater "Fundamentals of Internal Medicine" Appleton-Century Publ., 1944)

COMPLICATIONS

The course of hypothyroidism is usually monotonous and devoid of any complications but occasionally, incidental infections (e.g., tuberculosis) to which hypothyroid patients are very susceptible, or myxedematous infiltration of vital organs, may unexpectedly complicate the course of the disease. The frequent occurrence of herniae, as well as the untoward effect of ill-advised therapeutic procedures have been discussed elsewhere.

DIAGNOSIS

Hypothyroidism is rarely diagnosed at birth but at the age of one or two months, the clinical signs: thickening of the skin, hoarseness of the cry, the facial expression and especially the protrusion of the enlarged tongue, usually raise the suspicion of congenital cretinism.

After the first year, the retardation of physical and mental development is quite definite. The appearance of the ossification points and the eruption of teeth are delayed and the infants do not learn to walk or talk. In severe cases, they behave like decerebrate animals, showing no signs of emotion or interest in their surroundings. Some are good-natured clowns, others are malicious and aggressive but this is less common. The characteristic pot-belly, prominent buttocks and scapular regions with their myxedematous infiltrates all help to formulate the diagnosis which must be made early before the damage becomes irreparable In infants the B.M.R is no reliable criterion but special emphasis should be placed on the delayed appearance of ossification centers

Mild cases of adult myxedema often elude recognition for many years. Here, the low B.M R is one of the best diagnostic indices; it falls to −40% in the complete absence of thyroid function. It is well to remember, however, that



Mongolism in a boy. 5-year-old boy with typical *eyes and facial expression*
(Courtesy of Dr E.-P. McCullagh.)

basal *metabolic rates of —10 to —15%* are frequently seen in normal individuals and therefore no B.M.R. should be regarded as definitely subnormal unless it is below —15%.

A BLOOD CHOLESTEROL of more than 250 mg./100 cc., especially if combined with a low B.M.R. is very suggestive, but not absolutely pathognomonic.

The glucose and especially the GALACTOSE TOLERANCE are increased while the BLOOD IODINE concentration is decreased.

A number of PURPORTEDLY SPECIFIC DIAGNOSTIC TESTS (oculo-cardiac reflex, Reid-Hunt's acetonitrile test on the patient's blood, electric impedance angle, excessive quinine sensitivity, increased *atropine sensitivity* of the heart, etc.) are all unreliable and we mention them here merely to warn against placing too much reliance on them.

From the differential diagnostic viewpoint possible confusion with CHRONIC NEPHRITIS OR LIPID NEPHROSIS is noteworthy, since in both conditions, the total blood lipids and the blood chol-



Mongoloid idiocy in a young girl. Note characteristic mongoloid eyes, normal skin and hair texture which distinguishes the mongoloid imbecile from *the hypothyroid cretin*
(Courtesy of Dr A. Pinto Viégas.)



Typical mongoloid idiocy in six-year-old negro girl.
(Courtesy of Dr J. J. Lobo.)

esterol are high, the albumin/globulin ratio of the plasma is inversed, there is a tendency to cardiac decompensation and edema and the urine may contain protein and casts. Even diagnostic treatment with thyroid preparations — which often helps to recognize the disease — is not particularly useful in this case since thyroid hormone improves diuresis in nephrosis also. Confusion of hypothyroidism with ARTHRITIS (occurrence of joint and muscle pains); MYOCARDITIS (cardiac enlargement and insufficiency); ADDISON'S DISEASE (low B.M.R. and muscular weakness with general torpor); MONGOLOIDISM (idiocy, stunted growth, cretinoid features) and especially PERNICIOUS ANEMIA, (pallor, puffiness of the face, lassitude), must always be kept in mind, yet the general clinical aspect of the patient, as well as the symptoms and signs discussed in the section on Clinical Course, usually permit the correct diagnosis.

PROGNOSIS

In the absence of treatment, hypothyroidism is a slowly progressive disease but finally — often after several decades — the patient loses his strength, the myxedematous infiltrations disappear, there is a pronounced loss of weight and "cachexia strumipriva" supervenes. The immediate cause of death is usually some pulmonary complication (often tuberculosis), a complicating renal or cerebral disease, or indeed, any type of, even mild, infection or intoxication which normal persons would readily resist

THERAPY

In the event of adequate THYROID THERAPY, all the symptoms and signs of adult myxedema disappear within a few weeks or months. It is good practice to proceed carefully, especially in patients who have arteriosclerosis or coronary disease because of the danger





Adult Myxedema. — A. Typical myxedematous facies before therapy — B. Same patient after thyroid therapy.
(Courtesy of Dr R.-W. Rawson.)

of precipitating a cardiac infarct. Any sign of cardiac malaise, which may develop during the treatment is an indication to proceed more gradually and temporarily to interrupt or decrease hormone treatment.

There is no justification for giving thyroxine intravenously since the action of the hormone is slow in any event. Thyroxine given orally has no advantage over desiccated thyroid and the latter is less expensive. In general 1.0-2.0 grains (60-120 mg.) of desiccated thyroid or 0.5 mg. of thyroxine is an adequate daily replacement dose in adult myxedema.

In children it is especially important to start treatment early. The daily dose should be raised from 0.1 grain (6 mg.) at 6 months to 1 grain (60 mg.) of desiccated thyroid at puberty.

It should be remembered that 1 grain of desiccated thyroid U.S.P. corresponds to 5 grains of the fresh gland and that the potency of the commercial desiccated thyroid preparations vary. It is essential, therefore, to base the dosage upon the iodine content of the thyroid preparation used. The dosages recommended refer to U.S.P. desiccated thyroid. (See: "Mode of Administration", p. 698.)

Since thyroid hormone acts slowly the effects of daily doses are cumulative; furthermore, a given dose is more effective in hypothyroid than in normal individuals. Thus the action of a single moderate dose may last about 10 days in normal, and 40 days in myxedematous subjects.

Implantation of thyroxine pellets is not advisable in patients with myxedema because the absorption rate is too slow.

3,5-DIIODOTHYRONINE has also been found effective in myxedema, but 50-75 mg./day are required in patients who respond adequately to 1 mg./day of thyroxine.

SPONTANEOUS HYPOTHYROIDISM IN ANIMALS

Before the introduction of iodine prophylaxis, hypothyroid goiters were quite frequently seen among domestic and wild animals, living in goitrous regions. Essentially, the symptomatology of spontaneous hypothyroidism is the same in man and animals, although myxedematous infiltrations occur only in certain species (e g , pig).

HYPERTHYROIDISM

(Synonyms Hyperthyroidism, Graves' disease, Basedow's disease, Flajani's disease, Toxic goiter, Exophthalmic goiter.)

DEFINITION

Hyperthyroidism is a condition in which the hormone production of the thyroid is sufficiently increased to produce detectable symptoms of overdosage.

The various clinical types (see section: "Classification") differ somewhat in their symptomatology and may be caused by different pathogenic mechanisms, yet their clinical manifestations are sufficiently similar to warrant a synoptic discussion under the common heading of "hyperthyroidism."

CLASSIFICATION

The subdivision of hyperthyroidism into various qualitatively different classes has not been very successful because of the frequent occurrence of intermediate types.

According to THYROID PATHOLOGY, we may distinguish

(1) *Exophthalmic goiter* (Graves' disease).

(2) *Toxic adenoma* (Plummer's adenoma)

(3) *Hyperthyroidism without goiter.*

The toxic goiter (which in turn may be diffuse or nodular) has been interpreted as resulting from the "Basedowification" of an originally asymptomatic goiter. The "toxic adenoma" of *Plummer* corresponds to the nodular variety of this type. Sudden manifestations of thyroid-hormone overdosage are not infrequent in patients who bore a simple goiter for many years. In the case of nodular goiters, this is often the consequence of treatment with excessive doses of iodine. The main difference between the toxic goiter and pure Graves' disease is that in the former, exophthalmos and tremor are usually absent, hypertension is common and the thyroid enlargement antedates the manifestations of hyperthyroidism

The so-called hyperthyroidism without goiter is rarely due to hyperfunction of a retrotracheal nodule or of an ectopic accessory thyroid; more frequently (especially in the male) it results from functional hyperactivity of the thyroid unaccompanied by a clinically detectable enlargement of the gland.

According to the AGE OF ONSET, we distinguish ·

(1) *Childhood hyperthyroidism*

(2) *Adult hyperthyroidism.*

In children, hyperthyroidism is comparatively rare. It differs from the corresponding disease of the adult in that the goiter is more constantly present, very vascular and free of nodules, the tachycardia is moderate (100-120), while the cardiac palpitations, exophthalmos and other ocular symptoms are frequently absent. Apparently, depending upon the severity of the condition, the somatic growth and general development of the children may be either inhibited or accelerated by hyperthyroidism. The course of juvenile hyperthyroidism is usually benign, about 60% of the cases recover spontaneously, although relapses are always possible.

According to the INTENSITY OF THE HYPERTHYROIDISM, we may distinguish :

(1) *Severe hyperthyroidism.*

(2) *Moderate hyperthyroidism.*

(3) *Latent hyperthyroidism* ("Formes Frustes").

This classification is self-explanatory but attention should be called to the fact that there are many borderline cases between the normal and the pathologic which are generally included in Group 3 as "basedowoid" conditions or "formes frustes" of hyperthyroidism. The transitory, slight increase in thyroid function seen in some women, at the time of puberty and during pregnancy, falls into this category, as does the "hyperthyroid constitution." The latter is characterized by slight exophthalmos, nervous irritability and a mild degree of thyroid enlargement, which are not progressive but remain at the borderline of normalcy throughout life. The "para-Basedow" or neuro-circulatory syndrome of Labbé is probably not a true hyperthyroidism since the B M.R. is normal and there are no pathognomonic manifestations of increased thyroid-hormone production, although there is exophthalmos, tachycardia and circulatory derangement.

According to ETIOLOGY, we distinguish between

(1) *Primary hyperthyroidism* (due to hyperfunctioning neoplasms of the gland; e g., toxic adenomas, functional carcinomas).

(2) *Secondary hyperthyroidism* (due to excessive thyrotrophin production by the pituitary; e.g , hyperthyroidism in acromegaly).

It will be noted that the terms "primary" and "secondary," used in this (endocrinologic) sense, are not in agreement with the classification of goiters recommended by the American Association for the Study of Goiter (see. p 715)

In many instances, the differentiation between primary and secondary hyperthyroidism is impossible in practice.

Among the unusual varieties of hyperthyroidism, the ACUTE FULMINATING TYPE, the CACHECTIC TYPE and the MASKED OR CARDIOTOXIC TYPE deserve attention. In the latter, the cardiac disturbances *are so prominent that the real* cause of the disease is masked under the picture of a primary heart disease. Several other varieties are named for an especially predominating manifestation; for instance the "OPHTHALMIC TYPE," the "CHRONIC THYROTOXIC MYOPATHY" (which simulates myasthenia gravis), the OSTEOPOROTIC TYPE, etc.

PATHOLOGIC ANATOMY

In typical Graves' disease, the thyroid *gland is more or less diffusely enlarged,* soft and very vascular. Its rich blood *supply accounts for the pulsation, thrill* and bruit which are often clinically detectable *in the thyroid region.* However, occasionally, the enlargement is *so slight that the gland cannot be palpated.* In other instances, more or less *circumscribed, adenoma-like nodules* develop within the diffusely enlarged gland.

Microscopically, the appearance of *the thyroid is essentially the same as in* other types of excessive hormonal activity, *such as compensatory hypertrophy* following partial excision, stimulation *by exposure to cold or thyrotrophin* injection. The follicles are irregular in *size and shape and contain little or no* colloid. Yet, there are exceptional instances *with abundant thyroid colloid.* The epithelium is high-cuboidal or even *columnar and is too hyperplastic to* fit smoothly into the follicular wall, so that *it is thrown into folds,* with papillary ingrowths encroaching upon the cavity. *The Golgi apparatus is hypertrophic* and there is an increased number of





Thyroid in Graves' disease. — A. Note papilloma-like proliferation of the epithelium and almost complete absence of colloid *in this goiter. The patient suffered from severe Graves' disease.* — B. Another region from the same thyroid. Note that here small follicular areas prevail. (Courtesy of Dr. T. Waugh.)



Thyroid in Graves' disease. Note almost complete absence of colloid, small follicles with high cylindric, epithelial lining-cells and lymphocytic infiltration
(Courtesy of Dr W Boyd.)





Thyroid in Graves' disease. — A. Massive cell structure due to almost complete absence of colloid in collapsed vesicles and great height of epithelial lining-cells Note also characteristic lymphocytic infiltration — B Another area of the same thyroid Note cauliflower-like excrescences of epithelial cells which invade the follicular lumen

mitochondria. The stroma may be cirrhotic and frequently contains lymph-cell infiltrates or even lymph nodules with germinal centers. Following spontaneous recovery the gland reassumes its normal histologic appearance.

After successful iodine medication there is intense colloid storage which often causes enlargement and tenderness of the thyroid. *Marine* believes that this distention by colloid causes temporary mechanical blockage of the pathways through which the hormone is discharged into the blood. However, eventually secretion is re-established at a higher level of pressure, hence, iodine therapy gives only transitory relief. It has been claimed that the alveoli of the toxic adenomas usually show no signs of colloid storage following iodine medication, and correspondingly, there is no clinical improvement; however, this is not the rule.

In some instances, the bulk of the thyroid tissue is normal or atrophic, but one or two hyperplastic, adenoma-like nodules exhibit the histologic characteristics similar to those described above, as typical of the entire gland in true Graves' disease. Nodular hyperplasias of this kind have been regarded as primary thyroid adenomas and are termed "toxic adenomas" if they result in hyperthyroidism.

About 75% of all cases of hyperthyroidism show the diffuse type of hyperplasia, although one lobe may predominate In most of the remaining instances, the histologic evidence of hyperplasia is more or less completely limited to macroscopically visible nodules.

In about 10% of all hyperthyroid patients, goiter is not clinically detectable, either because the hyperplasia does not result in any noticeable thyroid enlargement, or — in rare instances — because the hyperplastic thyroid tissue is ectopic In such patients the possibility of lingual, thyroglossal, intrathoracic, retrotracheal and accessory cervical or ovarian goiters must be kept in mind.

INCIDENCE

Accurate data concerning the GENERAL INCIDENCE of hyperthyroidism are difficult to obtain because many patients do not seek medical advice unless some complication arises, while others are treated by private physicians whose data are not available for statistical analysis. The records of the large hospitals give contradictory results, since in communities in which the medical and especially, the surgical staffs of the large hospitals specialize in this disease, the number of admissions is very high, while in other communities, such cases are less frequently treated in the hospitals. However, it is estimated that about 20% of the thyroid adenomas eventually become toxic.

Hyperthyroidism may occur at any AGE but is most frequent in the third and fourth decades.

The disease is much more frequent in the female than in the male SEX but the preponderance of females is not as marked as in myxedema. It is estimated to be 4:1 in regions in which goiter is not endemic and 4 3 in an endemic goiter region (Michigan).

PREGNANCY and hyperthyroidism do not necessarily influence each other. Yet some hyperthyroid women are unusually fertile, while others are sterile. Furthermore, a pregnancy may either aggravate or ameliorate the course of a pre-existing hyperthyroidism, depending upon factors which are not yet understood. There is no convincing evidence to show that the offspring of hyperthyroid women suffer in any way from the disease of their mothers

The mild and transitory hyperthyroidism occasionally seen in the course of an otherwise normal pregnancy has already been mentioned It may be attributable to hyperfunction of the an-

terior-lobe (increased thyrotrophin production?) characteristic of the gestation period.

The rôle of HEREDITARY predisposition is rather doubtful. It has been stated that certain individuals have a "Graves' constitution," *in the form of an inherited predisposition to the development of hyperthyroidism.* Several cases of Graves' disease in the same *family have repeatedly been observed.* However, the claim that the Japanese and East Indians do not suffer from hyperthyroidism is unfounded. No race appears to be immune.

PATHOGENESIS

As mentioned in the section on Classification, certain types of hyperthyroidism appear to be PRIMARY and due to causes inherent in a hyperfunctional neoplasm of the thyroid itself. Their pathogenesis is shrouded in the mystery of tumor formation in general.

A good deal of evidence has accumulated concerning stimuli which can produce SECONDARY thyroid hyperplasia (*see: Stimuli Influencing Thyroid* Structure, pp. 708-710) via the pituitary. *Among these, the action of functional* ANTERIOR-LOBE NEOPLASMS is most readily understandable, but of comparatively little clinical significance. Only few of the primary anterior-lobe tumors cause secondary hyperthyroidism and the vast majority of the pertinent cases can not be explained on this basis.

The stimulation of thyrotrophin production by various types of exposure is probably of much greater clinical import Many cases of hyperthyroidism develop following some type of NON-SPECIFIC STRESS (e g., sudden mental shock, infections, intoxications, trauma, menarche, pregnancy, menopause).

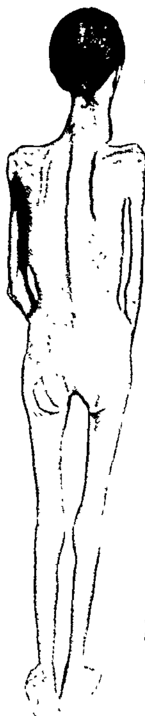
Iodine deficiency results in a compensatory increase in thyrotrophin production, with *accumulation of colloid* in the thyroid but no signs of hyperthyroidism. However, if LARGE DOSES OF IODIDES *are administered at this time,* an excessive amount of thyroid hormone may be produced from hormone *precursors stored in the colloid. This* could explain the pathogenesis of the "*iodide Graves' disease.*"

The so-called "THYROID CRISES" *which sometimes occur following thy-*roidectomy in patients with Graves' disease, have been considered to result from sudden flooding of the organism with thyroid hormone, liberated from the remaining traumatized thyroid tissue, however, this is not proven. Since the exophthalmos may persist or even increase after thyroidectomy, one *should consider the possibility that the* thyroid crises (as the exophthalmos) could be the immediate result of a post-operative increase in thyrotrophin production. Yet thyroid medication, which normally decreases thyrotrophin secretion rarely improves the exophthalmos in such thyroidectomized patients.

It must be admitted that at present the etiology of Graves' disease is still insufficiently understood. We know nothing about the reasons responsible for the persistently excessive production of thyrotrophin following a single, pathogenic *stimulus, nor* do we have any definite proof that all cases of *typical Graves' disease are due to this* mechanism.

CLINICAL COURSE

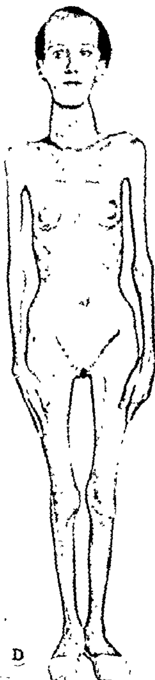
State. — The appearance of the typical hyperthyroid patient is mainly characterized by exophthalmos, tremor and sweating, which combine to give an impression of great emotional excitement and even terror These patients are extremely sensitive to various intercurrent infections, especially tuberculosis, and because of the greatly increased B M.R. *even short periods of fasting* are badly tolerated. In women, the *manifestations of the disease are often* aggravated premenstrually.



Severe Graves' disease. — A., B., C. and D. 32-year-old woman exhibiting extreme emaciation, atrophy of the breasts, loss of sexual and non-sexual hair, B M R +100%, blood cholesterol, 128 mg %, amenorrhea and auricular fibrillation

(Courtesy of Dr A -B de Ulhôa Cintra)

C



B

Note the almost complete absence of ocular manifestations in the presence of a very large, asymmetric, nodular goiter



Graves' disease. Note mild exophthalmos and goiter
(Courtesy of Dr A Pinto Viegas)



Graves' disease. Note marked exophthalmos and small goiter
(Courtesy of Dr A Pinto Viegas)

Metabolism. — The B.M.R. is characteristically elevated in hyperthyroidism and ranges between +20 and +100%. B.M.R. values below +15% are not to be regarded as definitely elevated; however, even this value may be high and accompanied by manifestations of hyperthyroidism in people whose normal B.M.R. is around −15%. Such low metabolic rates are often familial and unaccompanied by signs of hypothyroidism.

In hyperthyroidism there is loss of weight and often slight hyperthermia as a result of which the daily maintenance requirement may be as high as 5,000 calories at rest.

There is a decreased CARBOHYDRATE and especially, galactose tolerance, which represents the counterpart of the picture characteristic of hypothyroidism. In some instances, this disturbance is so severe that spontaneous glycosuria ensues and it is estimated that frank diabetes mellitus occurs in about 2% of all instances of typical hyperthyroidism. These disturbances have generally been interpreted as due to the inability of the liver to store glycogen but there may be other factors involved. It has recently been shown that thyroid hormone overdosage causes damage to the Langerhans islets of the pancreas and may induce permanent diabetes in animals (See: p. 502-504.)

The total LIPID content of the body is low, since hyperthyroid patients are usually lean, especially if the B.M.R. is very high. The blood cholesterol is normal or slightly subnormal (100 mg/100 cc or less). However, this fall in blood cholesterol is not nearly as constant or pronounced as the rise in hypothyroidism.

The NITROGEN balance becomes negative if the food intake is inadequate, during a "thyroid crisis" or as a result of continuous vomiting which is not uncommon among these patients. The



Exophthalmos of Graves' disease. Note expression of terror or anger, mainly due to extreme lid retraction, which accentuates the exophthalmos (A P measurement of bulbs 26 mm). B.M.R. was as high as +64% before thyroidectomy, this picture shows patient 15 months postoperatively when the B.M.R. was about normal (never below +2%), yet exophthalmos tended to become worse. Edema and ocular muscle imbalance minimal in this instance.
(Courtesy of Dr E.-P. McCullagh.)

plasma albumin/globulin ratio is deranged owing to an increase in the albumin fraction. Here, again, the change is the reverse of that characteristic of hypothyroidism.

The most prominent disturbance in SALT AND WATER METABOLISM is the derangement in the metabolism of *iodine*. We have already referred to the technical difficulties involved in the determination of the small quantities of iodine present in biologic materials. This explains the great variations in

the results reported. In one carefully examined series, the average iodine content of the blood in normal persons (kept on a low iodine diet) was 4γ/100 cc. whole blood and 7.1γ/100 cc. plasma. The corresponding figures, in 10 markedly hyperthyroid patients, were 10 and 18γ, respectively. It appears that approximately 95% of the total blood iodine is in the plasma, both in normal and in hyperthyroid individuals. Were it not for the difficulties of the pertinent analytic procedures, the blood iodine value would probably furnish a better diagnostic criterion than the B.M.R.

Patients with exophthalmic goiter usually have a markedly negative iodine balance; yet the iodine-poor thyroids of hyperthyroid patients have a particular avidity for iodine. This may be demonstrated by the iodine tolerance test (low blood-iodine curves following ingestion of the element), or by administering radioactive-iodine and subsequently estimating its concentration in the thyroid.

The *potassium, calcium, sodium* and *phosphorus* content of the blood do not show any characteristic deviation from the normal.

There is no very typical disturbance in *water* metabolism except the changes which are the direct result of the increased B.M R., or the increased secretory activity of the various excretory glands. Occasionally there is *periorbital and pretibial edema* of the skin. Not infrequently the *Robinson, Power and Kepler* test (see . Hypocorticoidism, p. 154) is positive, perhaps because hyperthyroidism causes "relative hypocorticoidism."

Growth and Bone Structure. — *In many hyperthyroid children there is a definitely increased somatic-growth rate although in severely cachetic patients the reverse may be true*

Blood Picture. — The blood picture of hyperthyroid patients is sometimes *normal but more often there is polymorphonuclear leukopenia with lymphocytosis.* The red-cell count is usually normal but there may be hypochromic anemia.

Cardiovascular System. — The PULSE rate is increased. *It is usually more than 100/minute and may be as high as 140.* In the absence of such *complications as auricular fibrillation, the pulse is usually regular. The tachycardia shows only a slight tendency to decrease under the influence of rest and sleep but rises considerably as a result of even slight emotional excitement.* The *parallelism* between the B.M.R. and the pulse rate is only approximate. The patients frequently complain of *cardiac palpitations* and *the beat of the apex is often so intense that it shakes the whole thoracic wall.* The heart sounds are usually very loud. There is often a systolic *murmur near the sternal border in the second or third intercostal space or above the apex.*

The most frequent ARRYTHMIA is auricular fibrillation; estimated to be present *in about 10-15% of all typical instances of hyperthyroidism.* It is more common in the so-called toxic adenomas than in *the typical exophthalmic goiter* Usually *it begins in the form of paroxysmal attacks which subsequently tend to become permanent. Except for cases with irreversible anatomic lesions in the myocardium, these functional disturbances respond well to thyroidectomy.* Extrasystolic arrythmias are less common

ANATOMICALLY the *more or less generalized cardiac hypertrophy is rarely striking* Actual pathologic lesions such as *arteriosclerosis of the coronary vessels, infarcts or "rheumatic carditis"* are frequent but have generally been ascribed to incidental causes. However, *in the light of recent experimental work, they could result from the hyperthyroidism itself.*

Upon fluoroscopic X-RAY examination, the most outstanding feature of the hyperthyroid heart is the extraordinary rapidity and amplitude of its contractions. The beat is so vehement that it tends to cause a pulsatory movement of the entire pulmonary hilum ("Danza hiliar" of the South American investigators). X-ray plates show an increase in the total cardiac shadow in about 50% of the cases. The arc of the pulmonary artery is especially prominent, thus giving the heart the typical mitral configuration. This is unaccompanied, however, by the enlargement of the left auricle, so characteristic of mitral stenosis.

Although there is no ELECTROCARDIOGRAM (E.C.G.) truly pathognomonic of hyperthyroidism, the following features are rather characteristic : sinus tachycardia, high voltage of the P wave (especially in leads 2 and 3) which is often wide, and a high T wave (especially in leads 1 and 2) with a diminution of the $\frac{R}{T}$ quotient. The R-T interval is usually shorter than would correspond to the degree of tachycardia Of course, if there are arrythmias, extrasystoles or auricular fibrillation, these will also reveal themselves in the electrocardiogram

The mean BLOOD PRESSURE is usually normal in Graves' disease although in the so-called toxic adenoma there is a certain tendency towards hypertension and of course, if a hyperthyroid patient coincidentally develops arteriosclerosis, this may independently cause a rise in blood pressure. However, in typical cases, the systolic blood-pressure is normal or only slightly elevated, while the diastolic pressure is diminished. The resulting rise in pulse pressure is partly due to the intensity of the cardiac contractions and partly to the diminished peripheral resistance caused by systemic vasodilatation. It often causes very pronounced pulsatory movements of the large cervical vessels and visible capillary pulsations.

The CIRCULATION TIME is characteristically decreased in hyperthyroidism and this has even been used as a diagnostic index. Thus if histamine is injected into the cubital vein of hyperthyroid patients, its presence is detected in the peripheral circulation after about 11 seconds as judged by the taste, and after 14 seconds as judged by skin-hyperemia. In normal controls, the corresponding figures are 15 and 18 seconds, respectively.

The various cardiovascular disturbances, described above, often cause various degrees of CARDIAC INSUFFICIENCY, among which dyspnea on exertion is the most characteristic. Severe congestive cardiac failure is comparatively rare except in very severe cases or in elderly patients with complicating cardiovascular disease. It is often preceded by auricular fibrillation.

ANGINA PECTORIS is rarely seen before 40 years of age. It usually occurs in men with pre-existent lesions of the coronary arteries and is claimed to be more common with toxic adenomas than with exophthalmic goiter (perhaps because the incidence of toxic adenomas is greater after the 40th year of age).

Lymphatic Organs. — Hyperthyroidism tends to cause enlargement of the lymphatic organs and especially of the thymus The mechanism of this effect is not yet understood.

Respiratory Organs. — The rate of respiration is increased, partly because of the rise in B.M.R. and partly because of the incomplete expansion of the thorax during each respiration. There is also a tendency towards irregular respiratory movements. The increased secretion of the respiratory mucosa may lead to "bronchorrhea" and sometimes there is a cough or dysphonia, without obvious anatomic cause. The occasional occurrence of "hyperthyroid asthma" attacks is attributed to an increased

tonus of the vegetative nervous system, which may lead to spasms of bronchial constriction.

Muscles. — Muscular tremor is a very constant manifestation of hyperthyroidism. Its frequency varies between 5 and 8 vibrations/second; its amplitude is usually small It may be demonstrated by asking the patient to hold out his hands horizontally in front of him, with the fingers spread. Some investigators ascribe this tremor to disturbances in the mesencephalic centers, but its pathogenesis is not yet understood. Sometimes there are choreiform or athetotic movements, paresias, paralyses or hemiplegias. The so-called "Basedowian pseudo-paraplegia" is a sudden sensation of weakness in the legs, which may cause the patient to collapse. It is ascribed to a debility of the quadriceps muscles. Such marked motor disabilities are comparatively rare, but generalized motor excitation, easy fatigability and diminution of muscular strength are common.

Often it is difficult to establish to what extent the motor disturbances are due to nervous or primarily muscular lesions, in severe cases with general cachexia, muscular atrophy is a frequent accompaniment of hyperthyroidism. It is sometimes accompanied by fatty degeneration of the muscle fibres.

Nervous System. — The great NERVOUS IRRITABILITY of hyperthyroidism is one of its most prominent manifestations These patients are almost continuously in motion and many of the motor disturbances, discussed in connection with the muscular system, may be primarily of nervous origin. There also is "amphotonia" of the vegetative nervous system, that is, increased irritability of both vagus and sympathetic. In the various organ systems the excitatory innervation appears to be especially stimulated (e g. the sympathetic in the cardiovascular system, the vagus as regards intestinal contraction, sweat secretion). Sometimes there is hyperesthesia of the skin over the thyroid region and the patients often complain of diverse neuralgias, migraines, etc., but otherwise there are no characteristic sensory disturbances.

The skin and tendon REFLEXES are often increased and there is great irritability of the cutaneous blood-vessels. Even slight rubbing of the skin, especially in the thyroid region, causes intense vasodilatation and there may be generalized vascular flushes, similar to those of the menopause.

The PSYCHIC INSTABILITY of hyperthyroid patients is also very typical. It may manifest itself by alternate periods of depression and manic excitation. The libido is frequently exaggerated in the beginning but greatly diminished in fully developed severe cases. There is often an intense boulimia with almost constant craving for food.

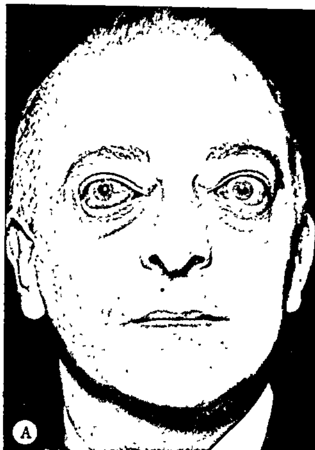
Sometimes the psychic disturbances become more serious. The patients are subject to spells of crying, fear and sometimes, agoraphobia. In extreme instances, it has been customary to speak of "Basedowian insanity" which often takes the form of true melancholia or manic-depressive psychosis. The term "thyrotoxic encephalopathy" has been used for a syndrome characterized by certain bulbar phenomena (dryness of the oral and pharyngeal mucosæ, disturbances in deglutition, mastication and speech) and loss of consciousness which sometimes develops into deep thyrotoxic coma. This syndrome is most frequent during the thyroid crises and usually terminates in death.

Sense Organs. — Among the ocular signs, the EXOPHTHALMOS is most prominent, but shows no close parallelism with the other manifestations of hyperthyroidism. It is usually absent in toxic adenomas; in Graves' disease it frequently appears only after surgical or X-ray therapy has decreased the excessive hormone production of the thy-

Ptosis in Graves' disease. — A. and B. In this instance ptosis and edema are more pronounced than exophthalmos (Courtesy of Dr E.-P. McCullagh.)



(Courtesy of Dr. E.-J. Kepler.)


A


B


C


D

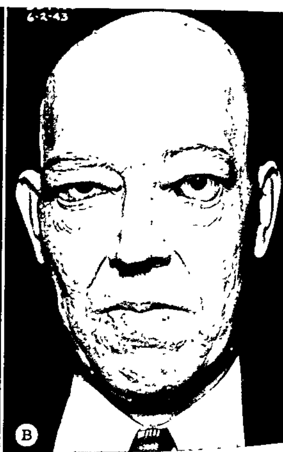


Progress of exophthalmos in Graves' disease. — A. Appearance two months following subtotal thyroidectomy (A P measurements of exophthalmos were O D 35 mm, and O S 33 mm) The absence of lid retraction gives appearance of much less exophthalmos than is actually present. — B. Five months postoperative. Tremendous 'bleb-like' edema of conjunctiva. (A P measurements O D 35 mm., O S 34 mm.) — C. Six weeks following orbital-decompression — D. Ten weeks after orbital-decompression — E. Ten months following orbital-decompression (A P. measurements O D 30 mm., O S 29 mm)
(Courtesy of Dr E.-P McCullagh)

roid. It often shows a lateral asymmetry affecting one eye only. Indeed, in the course of the disease, the exophthalmos may regress on one side and become more prominent on the other Sometimes it is so severe that corneal ulcers, panophthalmia or even complete luxation of the eyeball results In severe cases, lateral palpebroraphy (suture of the eyelids) or orbital-decompression may be necessary in order to protect the eye.

The pathogenesis of the exophthalmos in Graves' disease is still incompletely understood It has variously been attributed to edema, vascular engorgement and fat accumulation in the orbital tissue, or to contraction of the smooth muscles of Muller and the aponeurosis of Tenon, due to sympathetic stimulation. That stimulation of the cervical sympathetic chain causes exophthalmos, while its transection often cures a pre-existing exophthalmos, seems to lend support to the latter theory; yet, it is doubtful whether in man the smooth muscles of the orbit are as important as in some experimental animals In any event, it is definitely established that the thyroid hormone does not produce exophthalmos directly since thyroidectomy tends to aggravate rather than to cure it, and in thyroidectomized animals, thyrotrophin is at least normally effective in causing protrusion of the eyeballs. Many investigators believe that the exophthalmos is due to a direct action (not mediated by the thyroid) of thyrotrophin upon the hypothalamic centers Thyroidectomy may enhance this effect by stimulating endogenous thyrotrophin production.







Exophthalmos improved by orbital-decompression. Severe exophthalmos after thyroidectomy for Graves disease, marked bulging of the eyelids, extreme proptosis and conjunctival edema, followed by striking improvement after bilateral orbital-decompression — A. Appearance of patient 13 months after thyroidectomy before orbital-decompression — B. 5 weeks after bilateral orbital-decompression — C. 6 months after bilateral orbital-decompression

(Courtesy of Dr E.-P McCullagh)

Other characteristic ocular manifestations of hyperthyroidism are usually designated by eponyms. These are the signs of:

(1) MOEBIUS: failure of convergence of the eyeballs when the patient looks at an object slowly approaching towards him. This is probably due to paresia of the muscles of convergence.

(2) VON GRAEFE: asynergia between the movements of the eyeball and upper eyelid so that the latter does not follow the eyeball when the patient looks up or down.

(3) STELLWAG: retraction of the upper eyelid which prevents complete closure of the eye, even during sleep (Stellwag 1), and rarity of winking (Stellwag 2).

(4) CLIFFORD: difficulty of reverting the upper eyelid.

(5) JOFFROY: failure of contraction of the frontal muscles when the patient looks upwards.

(6) ENRROTH: edema of the palpebræ.

(7) JELLINEK: brownish pigmentation of the palpebræ causing a periorbital, dark circle.

(8) DALRYMPLE: fixity of gaze, due to increase in palpebral aperture and weakness of oculomotor muscles

(9) TOPOLANSKI vascular congestion of the pericorneal region, up to the insertions of the rectus muscles.

(10) ROSENBACH: fine fibrillar tremor of the upper eyelid, sometimes accompanied by blepharospasmus

(11) SAINTON · nystagmus in the event of lateral movement of the eyeball.

None of these ocular manifestations are in themselves pathognomonic and all of them never occur in the same patient, but if several are obvious, they assume diagnostic significance, especially when facilities for laboratory tests are not available.

As part of the general increase in the glandular secretions, tear secretion



Exophthalmos in Graves' disease. Note unilateral development of exophthalmos.
(After W M Yater Fundamentals of Internal Medicine Appleton-Century Publ 1944)

is often excessive in hyperthyroid patients.

Digestive System. — The usually excessive appetite may give way at times to severe anorexia with persistent vomiting and diarrhea. The latter has variously been ascribed to increased intestinal motility and secretion or to the achlorhydria, which is frequent in hyperthyroidism. Between the periods of diarrhea, the patient may be constipated

Hepatic damage is frequent in hyperthyroidism, it may reveal itself by hepatomegaly and impaired liver function tests. Icterus is rare and if present suggests a poor prognosis.

Skin and Appendages. — The warm and wet hyperemic skin is a very

constant diagnostic sign in hyperthyroidism. The cutaneous hyperemia becomes particularly obvious, under the influence of even slight emotional stimuli. The texture of the skin is usually fine. Sometimes there may be depigmented areas of vitiligo or more or less diffuse brownish pigmentation, in which the mucous membranes do not participate (difference from Addison's disease). The rather common periorbital pigmentation has already been mentioned.

Frequently, there are trophic disturbances in the NAILS, namely : a concave surface (as in hypochromic anemia), extreme shortness of the nail and irregularity or concavity of the line of separation between its adherent and free part.

The HAIR is usually very fine and it may show anomalies of pigmentation. Sometimes there is precocious greying of the hair in the temporal regions. At the onset of severe hyperthyroidism, there is a tendency for the axillary and pubic hair to fall out

The occasional occurrence of palpebral and pre-tibial SKIN EDEMA has been mentioned previously.

Urinary System. — Sometimes protein in the urine and increased diuresis suggest renal involvement, but as a rule hyperthyroidism does not produce any characteristic changes in the kidneys.

Sex Organs. — In severely hyperthyroid women, atrophy of the breasts, oligomenorrhea or even complete amenorrhea with sterility may occur; menorrhagias are much less common. In very mild cases, however, libido and fertility have been claimed to be increased.

In men, the influence upon the sex organs is less obvious, although sometimes there is gynecomastia and in severe cases, complete impotence is almost the rule.

COMPLICATIONS

The most important complication in hyperthyroidism is the so-called "THYROTOXIC CRISIS." This represents a sudden exacerbation of all symptoms with a marked increase in pulse rate (up to 140-160 minute), intense diarrhea, nausea, loss of weight, fever, pronounced rise in B.M.R., extreme excitation combined with great physical debility, sometimes "thyrotoxic encephalopathy" (see p. 754) and auricular fibrillation. These crises are frequently elicited by very traumatizing, partial thyroidectomies and occasionally even by excessive X-ray treatment of the thyroid, without suitable preparation of the patient (see : "Therapy", on p. 762). Such thyroid crises do not respond to any kind of therapy and frequently cause death from exhaustion or cardiac failure. Fortunately they are now very rare since suitable preoperative measures (iodine, thioureas, etc.) have come into common usage.

Other factors complicating the course of hyperthyroidism are FOCI of infection; they should be rapidly eliminated since they increase the severity of the disease.

Prolonged hyperthyroidism represents a great strain for the cardiovascular system and may result in DILATATION OF THE HEART WITH AURICULAR FIBRILLATION, as stated above

The various complications of exophthalmos, such as EDEMA OF THE CONJUNCTIVA AND CORNEAL ULCERS, have already been mentioned

The goiter may cause PRESSURE UPON THE RECURRENT LARYNGEAL NERVE and result in partial or total paralysis of the vocal cords, with hoarseness or even alarming respiratory difficulties. However, these complications are more common following operative interventions and direct surgical trauma to the laryngeal nerves.

The occasional combination of hyperthyroidism with ACROMEGALY, ADDI-

SON'S DISEASE OR DIABETES MELLITUS deserves only cursory mention. It is noteworthy, however, that signs of HYPER- and HYPOTHYROIDISM may occur simultaneously in the same patient. Thus, for instance, the exophthalmos characteristic of hyperthyroidism may persist, or even increase following a partial thyroidectomy, diminishing thyroid function to the point where myxedematous infiltrations begin to develop. Such complications have erroneously been ascribed to the production of abnormal thyroid hormone derivatives and were described as "dysthyroidism"; they are now more commonly attributed to increased thyrotrophin secretion.

DIAGNOSIS

The diagnosis of hyperthyroidism rarely causes difficulties in fully developed cases. In these, loss of weight, exophthalmos, goiter, tachycardia, sweating, psychic instability, tremor, an increased B.M.R and a high blood iodine level help to recognize the disease. However, several of these manifestations may be absent and especially incipient or masked types of hyperthyroidism can readily be overlooked. In such cases, the warm, moist skin, the tremor of the extended fingers, the decreased carbohydrate (especially galactose) tolerance curve and the efficacy of diagnostic iodine or thiourea treatment may help to recognize the true nature of the disease.

A number of other SUPPOSEDLY SPECIFIC DIAGNOSTIC SIGNS (ocular-cardiac reflex, Reid-Hunt's acetonitrile test on the patient's blood, electric impedance angle due to increased electric resistance, decreased quinine sensitivity, decreased atropine sensitivity of the heart, etc.) are all unreliable and we mention them here merely to warn against placing too much reliance upon them. The same is true of the so-called *Goetsch test*. It is based upon the fact that in hyperthyroidism the intramuscular administration of adrenaline may cause an abnormally pronounced rise in the B.M.R., tachycardia and a "widening of the pulse pressure" due to a rise in systolic, with a drop in diastolic pressure. The test is dangerous and not pathognomonic. The *Goetsch skin reaction* (abnormal local vasomotor responses to adrenaline) are likewise not specific.

From the differential diagnostic point of view, confusion with early pulmonary TUBERCULOSIS is noteworthy. The latter may be accompanied by tachycardia, nervousness, loss of weight and a slight increase in body temperature; however, the B.M.R. remains close to normal and other characteristic signs of hyperthyroidism are likewise absent. Certain RESPIRATORY NEUROSES, CARDIAC DECOMPENSATION, NEUROCIRCULATORY ASTHENIA and the LEUKEMIAS and POLYCYTHEMIAS with their characteristic cardiac manifestations and increased B.M.R. may likewise raise diagnostic problems. It is well to remember that in VASOMOTOR NEUROSIS the hands are usually cold while in hyperthyroidism they are warm. Since hyperthyroidism tends to cause hyperglycemia and even glycosuria, care must also be taken to differentiate instances with markedly impaired glucose tolerance, from true DIABETES MELLITUS.

PROGNOSIS

It is difficult to make any generalizations concerning the prognosis of hyperthyroidism because of the great individual variations in the course of the disease. However, in general the prognosis as to life is favorable. Many patients do not even consult a physician until several years after the onset of the disease and a duration of one or two decades without any treatment is by no means exceptional. Long lasting spontaneous remissions are common.

The prognosis is definitely more serious in male than in female patients. It

constant diagnostic sign in hyperthyroidism. The cutaneous hyperemia becomes particularly obvious, under the influence of even slight emotional stimuli. The texture of the skin is usually fine. Sometimes there may be depigmented areas of vitiligo or more or less diffuse brownish pigmentation, in which the mucous membranes do not participate (difference from Addison's disease). The rather common periorbital pigmentation has already been mentioned.

Frequently, there are trophic disturbances in the NAILS, namely . a concave surface (as in hypochromic anemia), extreme shortness of the nail and irregularity or concavity of the line of separation between its adherent and free part.

The HAIR is usually very fine and it may show anomalies of pigmentation. Sometimes there is precocious greying of the hair in the temporal regions. At the onset of severe hyperthyroidism, there is a tendency for the axillary and pubic hair to fall out

The occasional occurrence of palpebral and pre-tibial SKIN EDEMA has been mentioned previously.

Urinary System. — Sometimes protein in the urine and increased diuresis suggest renal involvement, but as a rule hyperthyroidism does not produce any characteristic changes in the kidneys

Sex Organs. — In severely hyperthyroid women, atrophy of the breasts, oligomenorrhea or even complete amenorrhea with sterility may occur, menorrhagias are much less common In very mild cases, however, libido and fertility have been claimed to be increased.

In men, the influence upon the sex organs is less obvious, although sometimes there is gynecomastia and in severe cases, complete impotence is almost the rule.

COMPLICATIONS

The most important complication in hyperthyroidism is the so-called "THYROTOXIC CRISIS." This represents a sudden exacerbation of all symptoms with a marked increase in pulse rate (up to 140-160 minute), intense diarrhea, nausea, loss of weight, fever, pronounced rise in B.M.R., extreme excitation combined with great physical debility, sometimes "thyrotoxic encephalopathy" (see p. 754) and auricular fibrillation These crises are frequently elicited by very traumatizing, partial thyroidectomies and occasionally even by excessive X-ray treatment of the thyroid, without suitable preparation of the patient (see : "Therapy", on p. 762). Such thyroid crises do not respond to any kind of therapy and frequently cause death from exhaustion or cardiac failure. Fortunately they are now very rare since suitable preoperative measures (iodine, thioureas, etc.) have come into common usage.

Other factors complicating the course of hyperthyroidism are FOCI of infection; they should be rapidly eliminated since they increase the severity of the disease.

Prolonged hyperthyroidism represents a great strain for the cardiovascular system and may result in DILATATION OF THE HEART WITH AURICULAR FIBRILLATION, as stated above.

The various complications of exophthalmos, such as EDEMA OF THE CONJUNCTIVA AND CORNEAL ULCERS, have already been mentioned

The goiter may cause PRESSURE UPON THE RECURRENT LARYNGEAL NERVE and result in partial or total paralysis of the vocal cords, with hoarseness or even alarming respiratory difficulties However, these complications are more common following operative interventions and direct surgical trauma to the laryngeal nerves.

The occasional combination of hyperthyroidism with ACROMEGALY, ADDI-

(1) PREOPERATIVE TREATMENT: because of the great excitability of hyperthyroid patients and the detrimental effect which any type of strain exerts upon the course of the disease, it is important to assure absolute, physical and mental REST by admitting the patient to hospital 2-3 weeks prior to the proposed intervention. In severe cases, bed rest and sedatives are necessary, otherwise minor movements about the room may be permitted in order to avoid muscular atrophy.

The DIET should be very nourishing (3,000-5,000 calories/day), rich in carbohydrates and methionine (or casein) in order to protect the liver against the hepatotoxic effects of hyperthyroidism. It must contain adequate amounts of vitamins (especially B-complex) and calcium (to prevent demineralization of the skeleton) In the event of achlorhydria, HCl should be administered before meals.

If IODINE is chosen as a specific therapeutic agent, it should be given in daily doses of at least 6-12 mg. Usually 5-10 drops of Lugol's solution is administered, in a little milk or water, three times a day before meals

Patients who previously never received iodine therapy almost invariably respond to it with a marked improvement of all clinical symptoms including a pronounced fall in B.M.R., which reaches its minimum after about 14 days of treatment The optimal response may persist for varying lengths of time but iodine resistance almost invariably develops eventually If a second course of iodine therapy is initiated following a month of rest, the patient may again respond favorably but usually the efficacy of this treatment diminishes and larger doses are required after repeated courses of therapy If a surgical intervention is to follow, it is therefore, best to undertake it at the moment when the patient has first developed a maximum beneficial response (usually at about the 14th day). Radio-I treatment is still in the experimental stage (Cf. p. 762.)

Only exceptional cases are permanently cured by iodine and some (especially those with exophthalmic goiter), may actually develop signs of hyperthyroidism as a result of it. It is important to resist the temptation of deciding against an operation in patients who appear to do very well for several weeks or months with nothing but iodine treatment, since usually they relapse and become unresponsive

Six to eight hours before operation, a carbohydrate-rich meal, with the usual dose of iodine should be given Some physicians prescribe hypertonic glucose intravenously, in order to combat hepatic damage and to supply an adequate source of energy.

In the event of even slight respiratory infections, the operation should be postponed for a fortnight.

Several THIOUREA DERIVATIVES (especially propyl-thiouracil) proved to be very effective as specific therapeutic agents in the preoperative medical treatment of hyperthyroidism Some physicians believe that the thioureas may even replace surgical interventions

The general principles involved in the action of thiourea derivatives have been discussed previously in other connections (see pp 692 and 710). It will be recalled that these compounds prevent the entrance of iodine into the thyroid and its consequent utilization for the synthesis of thyroid hormone As a result of this, the anterior-lobe produces an increased amount of thyrotrophin in a vain effort to compensate for the loss, there is hyperplasia of the thyroid but no rise in thyroid hormone production

Thiourea, as well as a number of its derivatives have been proven to possess antithyroid actions Such compounds are for instance

is most favorable in children in whom even spontaneous cures are not rare, while in adults, complete disappearance of the manifestations, without therapy, is quite exceptional.

With toxic adenomas, cardiac complications are more frequent than in exophthalmic goiter but the latter predisposes more to the dreaded thyrotoxic crises. The over-all prognosis of the two main types is, therefore, approximately the same.

The thyrotoxic crises may occur spontaneously or may be induced by ill-advised therapeutic procedures. Their mortality rate is very high, since they are almost entirely resistant to any type of treatment.

Sudden excessive loss of weight, icterus or other manifestations of hepatic complications and especially, severe psychic disturbances such as the thyrotoxic encephalopathy, almost invariably presage death

In the hands of experienced surgeons the postoperative prognosis is good if the patient is suitably prepared and not iodine resistant; yet relapses may occur. The prognosis of treatment with iodine or thioureas is discussed below (see Therapy).

THERAPY

The therapy may be internal, surgical, radiologic or — most frequently — based on a combination of these procedures.

Exclusively Medical Treatment. — Only in few instances is there any justification for the exclusively medical treatment of hyperthyroidism The very mild — and often transitory — hyperthyroidism of children and pubertal pregnant or menopausal women, may be treated in this manner and, of course, only this or X-ray treatment can be employed if the patient refuses operation, or is a very bad surgical risk Yet, as soon as the patient acquires resistance to internal therapy, it is useless to continue with it. Even severe diabetes or cardiac decompensation are no absolute contra-indication to surgical therapy, as long as judicious treatment is assured during the preoperative period: both these complications often show dramatic improvement following subtotal thyroidectomy. On the other hand, very severe exophthalmos may render surgical therapy inadvisable, since it is often aggravated further by thyroidectomy and serious ophthalmic complications may ensue.

In principle, the internal therapy of hyperthyroidism is based upon physical and mental REST, a suitable, abundant DIET (rich in carbohydrates, calcium and vitamins), IODIDES or THIOUREA derivatives and the administration of SEDATIVES (e g., phenobarbital and sodium bromide). Essentially the same type of internal therapy is to be prescribed in patients as a preparation for subsequent thyroidectomy and hence, we shall discuss its details in connection with the more commonly employed surgical treatment. (Cf. p 763.)

Radioactive iodine is highly recommended by some. Its advantage is that a permanent cure is often affected by a single oral dose. Care must be taken however, not to produce hypothyroidism by overdosage

Some physicians claim to have obtained beneficial results with SYMPATHETIC DEPRESSANT DRUGS, (e g, ergotamine tartrate), SODIUM BROMIDE or QUININE, but all these drugs have been largely displaced by the discovery of the

of the hyperfunctional thyroid. This must never be an emergency intervention in the presence of threatening symptoms, since at this time it may precipitate a thyrotoxic crisis. The intervention should always be preceded by suitable preparatory medical treatment with iodine or thioureas.

It is best to consider separately: preoperative, operative and postoperative treatment

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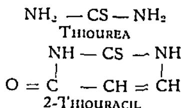
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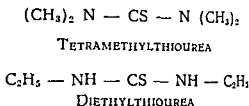
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Therapy with thioureas should start with a dose sufficiently high to free the patient rapidly of the manifest hyperthyroidism. After this is accomplished, a surgical intervention may follow with greater safety. If, however, treatment is to remain purely internal, the dose is diminished to a much lower maintenance level. To accomplish this 0.2 gm. of thiouracil given every 8 hours is usually adequate for initial detoxification and 0.2 gm. per day for maintenance of the euthyroid state. Propylthiouracil requires approximately half of this dosage. Under the influence of such treatment the B.M.R. usually

RaI ADMINISTERED TO PATIENT IN MICROCURIES

100 80 60 40 20

20 40 60 80 100 120 140 160

RaI EXCRETED IN URINE IN MICROCURIES

THIOURACIL 0.8 GM. DAILY

R. W. Rawson et al. J. Clin. Investigation *24*, 869 ... The plain ... intake, those below that line, iodine excretion. The stippled columns indicate ad... of ordinary sodium iodide. ... Note that before thiouracil treatment almost all the exogenous iodine was retained, while after therapy it was almost completely eliminated.

drops to about + 15% after some three weeks of treatment. The drug is effective both in toxic adenoma and in exophthalmic goiter, but perhaps less so in the former. Following preliminary treatment with iodine, subsequent administration of thioureas acts slowly until the stored thyroid iodine is consumed because the thioureas merely prevent the utilization of exogenous iodine for the synthesis of thyroid hormone.

However, several investigators claim that pretreatment with iodine does not delay the response to thioureas, provided the iodine is not discontinued. Indeed — especially as a pretreatment for surgery — it appears highly advisable to use thioureas simultaneously with iodine. The effect of these drugs on the thyrotoxicosis tends to be additive, and furthermore, the iodine coun-



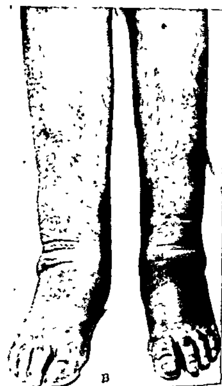




Effect of iodine and thiouracil in Graves' disease. — A. Histologic aspect of thyroid in Graves disease before therapy. Note proliferating hyperplastic epithelium. — B. Effect of thiouracil treatment. Note further increase in thyroid proliferation and hyperplasia. — C. Effect of combined treatment with thiouracil and iodine. Note that thyroid atrophy can be accomplished with iodine in spite of thiouracil treatment. This is noteworthy, since thiouracil impedes the entrance of iodine into the thyroid. *(Courtesy of Dr. R.-W. Rawson.)*



A



B

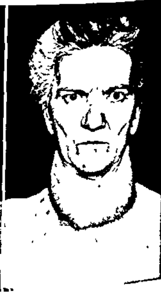
Thyroidectomy for Graves' disease. — A. and B. 40-year-old woman 6 months after thyroidectomy for typical exophthalmic goiter She developed marked edema of the face and legs Note also local hirsutism on legs and persistence of exophthalmos She also suffered from diplopia
(Courtesy of Dr E -B del Castillo)



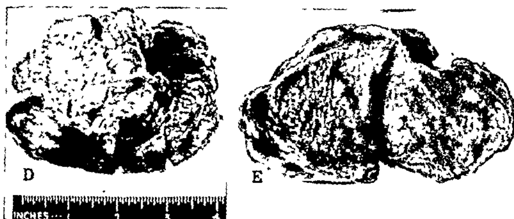
C



C



Graves' disease treated with thiouracil. — ment after 7 months of thiouracil treatment of thiouracil treat



— D. and E. Nodular thyroid removed from patient shown in Figs A to C — F. Histologic appearance of thyroid after one year of thiouracil treatment The patient took Lugol's solution (XV gtts 3 times a day for one month prior to removal of one thyroid lobe) There was extreme thyroid enlargement during thiouracil therapy, but the gland shows striking absence of hyperplasia (such as is seen after shorter treatment with thiouracil alone) and marked colloid retention — G Histologic appearance of thyroid removed by a second lobectomy, following additional 10 months of thiouracil treatment The patient again took Lugol's solution during the last month prior to surgery Note again colloid retention and absence of hyperplasia (presumably due to iodine medication)

(Courtesy of Dr E.-P McCullagh)

teracts the thyroid-enlarging effect of the thioureas. This is all the more remarkable since these antithyroid drugs prevent the entrance of iodine into the thyroid (clearly shown by radio-iodine studies). Apparently iodine exerts two distinct actions on the thyroid: (1) an anti-goitrogenic effect, (2) participation in the synthesis of thyroxine. Only the latter effect — which is detrimental in thyrotoxicosis — is prevented by thioureas.

Theoretically, thioureas should aggravate the goiter, in the anatomic sense, due to excessive thyrotrophin production; usually an enlargement of the thyroid is actually noted in spite of the functional improvement, but often there is at least a transitory diminution in thyroid size. The exophthalmos should also become worse for the same reason, but here again the results are variable: it may be aggravated, improved, or remain unchanged by the thioureas

The cardiac and metabolic manifestations of hyperthyroidism, on the other hand, are almost invariably and very significantly improved by thiouracil. In many instances, treatment has been continued for many months after which, quite frequently, administration of the drug could be discontinued without recurrence of the symptoms. Available statistics do not yet permit stating with finality . how long treatment should be continued, when to use surgical therapy; in what cases (if ever) these drugs can replace subtotal thyroidectomy, etc.

Undeniably, there are dangers involved in the administration of thioureas; among these, the development of the sometimes fatal agranulocytosis is especially noteworthy It is estimated that agranulocytosis occurs in 2.5% of the thiouracil-treated cases but only few of these die if the treatment is immediately discontinued when the first alarming signs appear. Blood transfusions are of little avail, since the foreign leukocytes are rapidly destroyed, but prophylactic penicillin treatment helps to raise the low resistance of the agranulocytotic patient to intercurrent infections. Patients treated with thiouracil should remain under constant observation, especially as regards their blood picture. None of the other possible complications are of comparable severity, but marked enlargement of the thyroid, pronounced exophthalmos and, in the event of excessive medication, hypothyroidism may be induced

In general it appears justified to conclude, however, that the introduction of thioureas represents a major progress in the therapy of hyperthyroidism The perfection of chemical methods for the detection of thioureas in the body-fluids will probably help to control dosage and formulate the indications and contraindications of this therapy.

(2) OPERATIVE THERAPY : The technic of the surgical intervention cannot be discussed here in detail but it is emphasized that more than in most other endocrine diseases amenable to surgical therapy, the personal skill and experience of the surgeon are of preeminent importance. Subtotal thyroidectomy must be performed with the minimum amount of trauma to the remaining thyroid and parathyroid tissue, in order to minimize the incidence of postoperative thyrotoxic crises or parathyroid tetany It is important to gauge exactly the amount of tissue to be removed so as to decrease the likelihood of postoperative myxedema due to excessive removal of glandular tissue or residual hyperthyroidism because of a quantitatively insufficient intervention. Special care must also be taken to avoid trauma to the recurrent laryngeal nerves.

(3) POSTOPERATIVE THERAPY. After the operation administration of iodine or the thioureas should be continued at the preoperative dose level for some time, to avoid a crisis Abundant quantities of glucose and sodium chloride solution should be given by the intra-

venous or rectal route. If parathyroid insufficiency develops it usually appears 2-3 days after the operation It calls for parathyroid hormone or calciferol administration together with abundant amounts of calcium.

If a thyrotoxic crisis ensues large doses of hypertonic glucose (30 cc of 60% solution or continuous intravenous drip of 5% glucose in physiologic saline) and corticoids should be administered intravenously. The patient is placed in an oxygen tent, and iodine or thiourea administration is continued. In the event of continuous vomiting, iodine must be given by the rectal or even intravenous route. Some physicians recommend covering the patient with ice-packs or even to give enemas of ice water. If there is great motor excitation, barbiturates and even morphine should be given in adequate amounts to insure rest In spite of all these therapeutic efforts, the prognosis of a severe thyrotoxic crisis is very grave.

X-ray Treatment. — The results of X-ray therapy are far more satisfactory in exophthalmic goiter than in toxic adenomas. In the former, approximately 50% cures can be expected under optimal conditions. However, the prognosis is less satisfactory, than that of surgical therapy, hence, X-ray treatment should be given only if there are serious contraindications to thyroidectomy Encouraging results have been obtained in patients in whom hyperthyroidism recurred followinq a transitory remission after subtotal thyroidectomy. X-rays are also recommended for iodine-resistant patients who are not considered good risks for surgical intervention.

SPONTANEOUS HYPERTHYROIDISM IN ANIMALS

Spontaneous hyperthyroidism is exceedingly rare among animals but certain cases of so-called heart death' in pigs have been shown to result from severe thyroid lesions conducive to thyrotoxicosis

TUMORS OF THE THYROID

DEFINITION

In the case of the thyroid, the distinction between hyperplasia and true tumors is somewhat artificial, since there are many transitions between the circumscribed, encapsulated, typical neoplasms, formed in an otherwise normal thyroid, and diffuse hyperplasia Thus, so-called "miliary" adenomas are often seen in the hyperplastic thyroids of patients with Graves' disease

For the convenience of clinicians, various types of benign neoplasms have been discussed under Simple Goiter, Hypothyroidism and Hyperthyroidism, depending upon the type of hormonal disturbance (if any) which they produce In this section we shall deal only with tumors whose most salient characteristics are those of a true independent thyroid neoplasm

CLASSIFICATION

The tumors of the thyroid may conveniently be classified as follows

(A) Adenomas
- (1) *Simple colloid adenoma*
- (2) *Papillary adenoma*
- (3) *Fetal adenoma* { *Solid or embryonal, Microfollicular*

(B) Carcinomas
- (1) *Metastasizing benign carcinomas*
- (2) *Papillary carcinomas*
- (3) *Small-round-cell carcinomas*
- (4) *Giant-cell carcinomas*
- (5) *Squamous-cell carcinomas*

(C) Sarcomas
- (1) *Fibrosarcomas*
- (2) *Lymphosarcomas*

(D) Teratomas

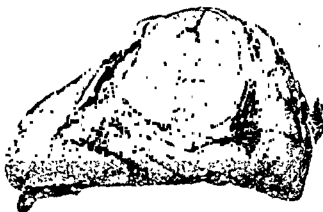
(E) Secondary (or Metastatic) Tumors

PATHOLOGIC ANATOMY

(A) Adenomas. — Most of the thyroid tumors, even carcinomas, originally exhibit the features of adenomas.



Thyroglossus duct cyst. Small cyst of the thyroglossus duct (left side of field), in its vicinity, several thyroid-like follicles surrounded by large amounts of lymphatic tissue. Note resemblance with lymphoid struma



Fetal adenoma of the thyroid. Woman, age 33 years, who committed suicide as a result of a manic-depressive psychosis Note sharp delimitation of small adenoma from surrounding normal thyroid tissue The neoplasm contains several large follicles, but most of its tissue is trabecular and of immature "fetal" appearance (as judged by examination under higher magnification)

(Courtesy of Dr L.-P Belanger)

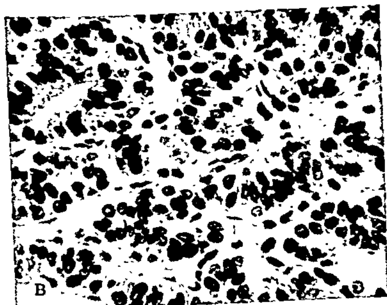
The SIMPLE COLLOID ADENOMAS are encapsulated, benign sometimes multiple tumors consisting of typical thyroid follicles, whose only abnormal characteristic is the great variability of their size The presence of exceptionally large follicles gives some of these adenomas a cystic character.

PAPILLARY ADENOMAS are poor in colloid and exhibit a distinctive papillomatous pattern They occur most frequently in the lateral portions of the normal thyroid and in "aberrant lateral thyroids" These adenomas have a great tendency to become malignant and then to metastasize in cervical lymph nodes, thus they may give the false impression of having originated in accessory lateral thyroids.

The FETAL ADENOMAS are subdivided into two groups The so-called EMBRYONAL ADENOMAS consist of epithelial trabeculae with little or no tendency towards follicle formation or colloid storage They are rather solid, parenchymatous epithelial growths In the FOLLICULAR ADENOMAS OF FETAL TYPE some acinus formation is observed but the follicles are small and lined by a flat or cuboidal epithelium As a rule, noteworthy accumulations of colloid are only seen in the periphery of these growths Both types of fetal adenomas tend to grow outwards from the center so that the youngest parts are in the periphery, while the center undergoes degeneration, often accompanied by liquefaction and cyst formation



"Fetal adenoma" of the thyroid. — A. Trabeculo-vesicular adenoma of the thyroid. The small struma was incidently found in a pseudohermaphroditic individual, it led to no disturbance in thyroid hormone production



— B. High magnification of a region from the same tumor, showing complete absence of follicle formation in this field. (Courtesy of Dr P. Masson)

(B) CARCINOMAS — The so-called "METASTASIZING, BENIGN CARCINOMAS" or "malignant adenomas" are neoplasms which exhibit all the histologic features of a benign tumor except that they invade blood capillaries and subsequently transplant themselves into distant organs. In some relevant instances — often referred to as "benign metastasizing strumas" — the thyroid contains a well-differentiated, apparently benign neoplasm usually of the colloid adenoma type. The metastases, which are often in bones, likewise reveal an apparently normal thyroid structure. However, if the primary growths are embryonal or fetal adenomas, the metastases tend to be of the same variety. Usually

there are no signs of hyperthyroidism but sometimes there is excessive hormone production by the almost normal thyroid tissue in the metastases. Occasionally, metastases of such seemingly normal thyroid tissue are found in the bones, lungs, liver and other viscera, even in patients whose thyroid appears to be entirely normal. In such cases, it may become extremely difficult to distinguish between the metastases of an undetectable primary thyroid neoplasm and a "metastasizing benign carcinoma" of an ectopic-thyroid. A seemingly metastatic nodule may, of course, represent a primary thyroid carcinoma in an ectopic gland.

In spite of their histologic structure, it is misleading to designate such neoplasms as benign. It is preferable to speak of a thyroid carcinoma without histologic indications of malignancy.

The PAPILLARY CARCINOMAS or papillary adenocarcinomas have the most *favorable prognosis among the malignant neoplasms of the thyroid.* They are similar to the benign, papillary adenomas but their cells undergo some anaplastic changes and have a certain tendency towards invasion of the stroma and capsule. They often contain *many mitotic figures and tend to* metastasize through the lymphatic route as well as by direct spread.

The SMALL-ROUND-CELL CARCINOMAS *of the thyroid have often been* confused with lymphosarcomas because of their negligible tendency towards acinus formation and because they consist of small, undifferentiated round cells with hyperchromic nuclei and many mitotic figures. Unlike in histologically similar lymphosarcomas, there usually is a past history of an adenoma which suddenly increased in size.

The GIANT-CELL CARCINOMAS are extremely anaplastic and contain many giant-cells with multilobed, hyperchromic nuclei. *They tend to spread* through the perivascular spaces and are highly subject to necrosis and degenerative changes. The acinar structure is almost entirely absent in these growths, hence they have often been confused with *giant-cell sarcomas,* but careful investigation reveals their origin from acini.

SQUAMOUS-CELL CARCINOMAS of the thyroid morphologically resemble those *found in other locations.*

The STRUMA POSTBRANCHIALIS — also known as small alveolar carcinoma, large-cell adenocarcinoma (*Langerhans*) or Hurthle cell tumor — is composed of comparatively small alveoli lined by one or several layers of large, irregularly polyhedral, cuboidal or cylindric *cells which usually* possess a clear cytoplasm with eosinophilic granules. They remotely resemble adrenal or liver cells but contain neither fat nor glycogen. Their abnormal structure suggests an unusual origin, perhaps from the parathyroid or carotid gland or the postbranchial body but this has *never been proven.* These growths vary in malignancy but are mostly benign. When they metastasize, the secondary foci exhibit the same *structure* as the parent tumors.

(C) SARCOMAS — Almost as many malignant tumors of the thyroid exhibit the characteristics of sarcomas as of *carcinomas.* In many cases, however, the differential diagnosis is almost impossible because of the great resem*blance between the true* FIBROSARCOMAS and the so-called "spindle-cell carcinomas" on the one hand, and between the LYMPHOSARCOMAS *and* the small-round-cell carcinomas on the other hand. Many other varieties (mixed, alveolar, fibrous, osteoid, *giant*-cell, etc., sarcomas) have been described but these are comparatively rare neoplasms. The sarcomas tend to *metastasize* through the blood stream and are extremely malignant

(D) TERATOMAS AND (E) SECONDARY (OR METASTATIC) TUMORS. — These rare thyroid tumors are of no endocrinologic significance.

INCIDENCE

Statistical data, concerning the GENERAL INCIDENCE of thyroid malignancy, are difficult to evaluate but the figures given by many authors who surveyed large series, indicate that about 1.5% of unselected cases of goiter prove to be malignant. Within the nodular variety of goiters, the incidence is slightly above 3%.

The AGE and SEX INCIDENCE of the adenomas have been discussed with the various types of goiters. Thyroid carcinomas occur most frequently in patients past 45 years of age, except the papillary carcinomas which are common in young adults.

Sarcomas of the thyroid usually appear after 40 years of age and have an equal sex-incidence.

PATHOGENESIS

It is estimated that more than 90% of all the thyroid carcinomas arise from originally benign adenomas. Since adenomas prevail in iodine-poor, goiter regions, it is very probable that iodine deficiency also has at least an indirect bearing upon the development of thyroid ADENOCARCINOMAS. It has been stated that in non-goitrous regions papillary types, and in goiter regions the non-papillary types of thyroid carcinomas prevail.

The SQUAMOUS-CELL CARCINOMAS of the thyroid probably originate from the thyroglossal duct, since no other component of the gland contains typical squamous epithelium; yet, in certain species, individual thyroid follicles are lined by cells resembling the stratified "pearls" of Hassall's bodies. Some of these growths may be of teratoid origin.

The SARCOMAS of the thyroid, as those of other epithelial organs are of stromal origin unless the growths are teratoids or secondary to extrathyroid sarcomas.

CLINICAL COURSE

The clinical course of malignant thyroid neoplasms is dominated by their tumoral, rather than their endocrinologic characteristics.

Sometimes they are encapsulated and their malignant nature is not suspected when they are removed. In other instances, their extremely rapid growth-rate and intense invasive and metastasizing tendencies cause death within a short time. The symptomatology is then governed by pressure upon the esophagus and trachea with consequent dysphagia and respiratory difficulties. This course is especially characteristic of undifferentiated carcinomas and tumors of the lympho- or fibrosarcoma types. The squamous-cell carcinomas, which likewise grow invasively, also tend to involve the regional lymph nodes.

HYPERTHYROIDISM is rarely associated with thyroid carcinomas. In patients with thyrotoxicosis, due to toxic adenomas or exophthalmic goiter, secondary malignant transformation of the thyroid is extremely rare. "One might almost say the thyrotoxicosis was insurance against cancer of the thyroid" (*Means*). On the other hand, the highly differentiated thyroid tissue found in the metastases of the so-called "benign metastasizing thyroid carcinoma" is obviously functional, since it may cause hyperthyroidism and maintain an adequate hormone supply even after complete excision of the orthotopic thyroid. Similarly, ovarian strumas have been known to cause hyperthyroidism even after subtotal thyroidectomy and these manifestations subsided following subsequent ablation of the ovarian growths

HYPOTHYROIDISM, due to destruction of the gland by a malignant thyroid tumor, does not appear to occur.



Thyroid carcinoma. 60-year-old woman who suffered from endemic goiter During last few months, she developed pain and manifestations of hyperthyroidism Biopsy revealed papilliferous thyroid carcinoma Multiple pulmonary metastases were detectable by X-rays
(Courtesy of Dr E B del Castillo)

DIAGNOSIS

The most valuable diagnostic criteria of malignant thyroid growths are: RAPID INCREASE IN SIZE, HARD CONSISTENCY, THE PRESENCE OF METASTASES, FIXATION TO ADJACENT STRUCTURES DUE TO ADHESIONS AND INVASIVE GROWTH. However, in about 15% of the pertinent cases, there is no indication of malignancy until the extirpated nodule is histologically identified

TENDERNESS is more characteristic of inflammatory lesions but may occur in cancer; FIXATION of the growth is equally characteristic of Riedel's thyroiditis, which also imitates the woody hardness of cancer

PRESSURE SYMPTOMS are much more common in malignancy than in thyroiditis but they may occur in either case

HYPOTHYROIDISM speaks strongly in favor of inflammatory lesions.

CALCIFICATION may be noted radiologically in malignant tumors, yet it is more characteristic of calcified adenomas. It will be kept in mind that if a growth is calcified, its hardness does not militate in favor of malignancy.

Temporary but marked IMPROVEMENT UPON X-RAY TREATMENT is definitely more typical of malignancy than of any other lesion, although Hashimoto's lymphoid thyroiditis is also radiosensitive.

RADIOACTIVE-IODINE as an indicator of metastases has its limitations because many metastasizing thyroid growths are so atypical that they do not selectively store it. However, in some instances it has proved useful, since after



Cancer of the thyroid. Note exulceration of the skin at the tip of the tumoral mass and involvement of a regional lymph node behind the ear-lobe
(Courtesy of Dr A Pinto Vilgas)



Cancer of the thyroid. The large thyroid cancer invades the various tissues of the neck region
(Courtesy of Dr A Pinto Viegas)

administration of radioactive-iodine, deposits of this element were detected by the Geiger counter in the metastatic nodules, thus facilitating localization of the latter.

BIOPSY is the safest procedure in most of the doubtful cases. Yet in the so-called "benign, metastasizing thyroid carcinomas," the histologic appearance is misleading.

PROGNOSIS

Only about 5% of the thyroid ADENOMAS eventually undergo malignant transformation but spontaneous cures are rare.

Among the CARCINOMAS the papillary type has a relatively favorable prognosis as it is often permanently cured by surgical removal, especially if this is followed by irradiation. Most other malignant thyroid-growths are rapidly fatal The SQUAMOUS-CELL CARCINOMAS as well as the LYMPHO-, GIANT-CELL- and SPINDLE-CELL SARCOMAS take a particularly malignant course and tend to recur following surgical removal or X-ray treatment. They usually terminate in death within a year after they first come to the physician's attention.

THERAPY

As far as possible, the therapy of choice is complete surgical removal of the growth: if necessary, together with the regional lymph modes, the sternomastoid muscle and even parts of the internal jugular vein. Should there be any doubt about the completeness of the removal, the operation must be followed by X-ray treatment. In general, adenocarcinomas are comparatively, and squamous-cell carcinomas totally, resistant to X-rays. On the other hand, papillary carcinomas and some of the small-cellular malignant neoplasms (small-cell carcinomas, lymphosarcomas) respond well at first although they tend to recur, either locally or in the form of metastases. For radiosensitive tumors 1,200 - 2,400 r, while for relatively radioresistant tumors, up to 4,000 r, should be administered in fractional doses. Irradiation may be followed by tracheitis or tracheal compression due to inflammatory lesions.

Hypothyroidism following extensive surgery is treated with thyroid.

Therapy with Radio-I is effective only in differentiated cancers.

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XI

HORMONES AND HORMONE-LIKE SUBSTANCES PRODUCED BY SIMPLE ENDO-EXOCRINE AND NON-GLANDULAR ORGANS

•

RENAL HORMONES

The only well established endocrine function of the kidney is concerned with the production of vasopressor substances. *Their rôle in adaptive processes* and in the pathogenesis of hypertension in man will be discussed in more detail in a separate chapter (see : "General-Adaptation-Syndrome", p. 837). We shall therefore limit ourselves here to a brief outline of the most important facts concerned with the physiology of the internal secretion of the kidney.

Historic Introduction. — It has first been shown (*Tigerstedt* and *Bergman*, 1898) that injection of kidney extracts can be followed by a rise in the arterial blood pressure in animals. Subsequent work revealed that if the lumen of the renal artery is partially constricted by *a clamp or ligature, persistent hypertension* ensues (*Goldblatt* et al. 1934) Indeed it was noted that no matter what method is used to decrease the intensity of the blood circulation through the kidney (see Methods, below), the blood pressure tends to rise owing to the discharge from the kidney into the venous blood of some vasopressor material.

It is still a strongly contested point whether the rise in pressor-substance production following partial constriction of *the renal artery is due to anoxemia*, a decrease in renal blood flow, a decrease in intra-renal blood pressure or a decrease in intra-renal pulse pressure.

Methods. — A number of experimental technics have been developed to produce persistent renal hypertension in animals. The following are of particular interest :

(1) *Constriction of the main renal artery* by means of a clamp or partial ligature.

(2) *Constriction of the aorta above the origin of the two renal arteries* In certain experimental animals, in which these two arteries originate from different levels, it suffices to put a *constricting ligature between the sites of origin of these two vessels* to produce hypertension, since such a procedure essentially corresponds to decreasing the arterial blood supply of one kidney. Similar ligatures placed below the origins of the two renal arteries *are not* conducive to a persistent rise in arterial pressure.

(3) *Compression of the kidney by silk, rubber, or cellophane wrappings* tightly placed around the surface

(4) *Considerable reduction in renal mass.* In certain animals (e g., rat) removal of one kidney and a considerable portion of the other suffices to raise the blood pressure; presumably because the small renal remnant undergoes a rapid compensatory hypertrophy which places it under pressure within its capsule. Since healthy kidney tissue — normally supplied with blood — antagonizes renal pressor material, the removal of normal kidney parenchyme may also play a rôle in this type of hypertension.

It is especially noteworthy, however, that complete ablation of both kidneys does not raise the blood pressure so that the hypertensive effect of renal interventions cannot be merely attributed to lack of kidney tissue as such.

Chemical Considerations Concerning the Origin of Renal Hypertension. — Investigations concerning the chemical nature of the renal pressor mechanism (*Houssay, Braun Menéndez, Page*, etc.) have revealed the following fundamental facts:

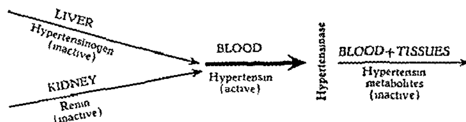
The kidney produces RENIN, a proteolytic enzyme, which itself is a protein. It is physiologically inert, but possesses the ability to break down a substrate-compound known as HYPERTENSINOGEN (or renin substrate), into an active vasopressor material HYPERTENSIN (or angiotonin)

Hypertensinogen is produced by the liver and belongs to the α_2-globulin fraction of the blood; it possesses a comparatively large molecule, which under the proteolytic influence of renin is split into a smaller polypeptide, namely, the above-mentioned hypertensin.

Curiously, other proteolytic enzymes can also transform proteins into similar pressor substances; thus the pepsin of the stomach acts upon hypertensinogen to form a pressor-substance known as "PEPSITENSIN" (*Croxatto*, 1942), whose properties are almost identical with those of hypertensin.

In various tissues — including kidney, plasma, erythrocytes, intestinal wall, etc — there is another enzyme HYPERTENSINASE (or angiotonase) which destroys hypertensin. It is possible that the antihypertensive effect of normal kidney tissue is partly due to hypertensinase or some similarly acting enzyme.

The following schematic drawing will help to visualize the interrelations between the various compounds involved in the production of renal hypertension:



As we have seen in the section on adrenaline derivatives, a number of PRESSOR AMINES, closely related to the hormone of the adrenal medulla, have vasoconstrictor properties and resemble hypertensin in their pharmacologic actions. It is tempting to speculate on the possibility that some of the amino-acid constituents of hypertensin may be related to the pressor amines. Indeed it must be admitted that, although the renin-hypertensin mechanism is most generally accepted as the basis of renal hypertension, some investigators believe that the kidney raises the blood pressure through the intermediary of amines, or yet other pressor substances, and that *renin production is of no great* physiologic significance.

Theories Concerning the Source of the Renal Pressor Hormone. — It is still not definitely known which cells in the kidney are responsible for the production of renin or other pressor substances. Within the walls of the afferent glomerular arterioles there are *certain* modified, smooth muscle cells which exhibit an epithelioid appearance.

Their cell bodies are roundish or polyhedral and they contain eosinophilic granules similar to those seen in the parathyroids and hypophysis. It has been assumed that these cells form a system, the JUXTAGLOMERULAR APPARATUS (*Goormaghtigh*), which participates in the maintenance of blood pressure through the production of vasopressor material.

However, certain facts appear to be opposed to this interpretation, as stated elsewhere (see: General-Adaptation-Syndrome). In rats, one kidney can be transformed into a purely endocrine organ by a constricting ligature placed between the origins of the two renal arteries; this happens only if the resulting intra-renal blood-pressure drop is sufficient to stop urine secretion in the kidney whose artery originates caudad from the ligature. Here the juxtaglomerular apparatus shows no sign of hyperactivity, in fact its cells may involute together with the glomeruli themselves. Nevertheless the blood pressure increases as a result of this operation. Since in these purely "ENDOCRINE KIDNEYS" only the convoluted tubules appear to remain in a functionally active state it is rather probable that they represent the source of the renal pressor material. In this sense the renal tubule could be regarded as a true endo-exocrine organ which, in addition to its internal secretory and excretory functions, also participates in the reabsorption of useful substances from the glomerular filtrate.

Stimuli Influencing the Course of Renal Hypertension. — NERVOUS STIMULI do not appear to play an important rôle in the production of hypertension through constriction of the renal vessels. It has been found that complete denervation of the kidney does not prevent the increased production of renin, and the consequent hypertension, if the renal artery is subsequently constricted. Even transplantation of a kidney (with its renal artery constricted), unto the cervical vessels of a nephrectomized dog proved to cause hypertension; in this case, of course, a direct effect of the nervous system upon the internal secretion of the kidney was excluded. The establishment of a cross-circulation, between a nephrectomized dog and one in whom the renal arteries had been constricted, causes hypertension in the recipient; this indicates that the pressor effect is carried solely through the blood stream.

Even the target organs upon which hypertensin acts do not have to be innervated in order to respond in a normal manner. Thus vasoconstriction can be produced in isolated, perfused organs (hind legs of a frog, ear of rabbit, tail of dog) by the addition to the perfusion fluid of venous blood from a kidney whose artery had been constricted.

The EXCRETORY FUNCTION of the kidney is likewise not essential for the production of renin. It has been possible to show that if the intra-vascular pressure in one kidney is sufficiently diminished to render glomerular filtration impossible, urine secretion ceases and yet the blood pressure rises. Under such conditions even transection of the ureter, between two ligatures, fails to counteract the hypertensive effect of the renal vessel constriction.

As previously stated, healthy kidney tissue with normal blood supply, antagonizes the pressor effect of renal hormones. Hence (at least in certain species, e.g., dog) constriction of only one main renal artery rarely produces marked [illegible] the [illegible] is re[illegible] vascularized renal tissue can destroy excessive amounts of renal pressor material. The presence of both kidneys does not interfere with the production of renal hypertension if constricting ligatures are placed on both renal arter-

ies or on the aorta above the origins of these vessels.

Following repeated injections of renin a phenomenon of TACHYPHYLAXIS develops, that is, subsequent injections of the material give progressively less marked pressor responses until complete — though transitory — insensitivity ensues. This phenomenon is presumably due to depletion of blood hypertensinogen, since it is prevented by exogenous administration of the latter. Sympathectomy or blockade of sympathetic ganglia by drugs (e g., tetraethyl ammonia) likewise prevents renin tachyphylaxis, but here the underlying mechanism is not clear.

HEPATECTOMY impedes the development of renal hypertension since it removes the source of endogenous hypertensinogen.

The HYPOPHYSIS and the ADRENAL CORTEX appear to play an important rôle in the development of renal hypertension. As explained in the chapter "The General-Adaptation-Syndrome" certain types of persistent hypertension in man may be due to increased formation of corticotrophin and corticoids. The widespread renal arteriolar lesions, produced by excessive amounts of these hormones, exert the same effect as a clamp on the main renal artery. Hypophysectomy or adrenalectomy decrease the vitality of experimental animals and hence diminish experimental renal hypertension, but if comparatively low doses of corticoids (not sufficient to produce hypertension in themselves) are administered to maintain such animals in good condition, then renal interventions can elicit pressor responses.

These observations are compatible with the view that the pituitary and adrenal cortex are not indispensable for the actions of the renal pressor substance but can augment the production of the latter due to their effect upon the caliber of the renal vessels.

The production of hypertensin from hypertensinogen is independent of all other body constituents since it occurs normally even in vitro under the influence of renin.

Clinical Implications of the Renal Pressor Mechanism. — It is rather likely that during the first stages, hypertension in man is usually "NEUROGENIC" as judged by the lability of the blood pressure. At this time vasoconstriction, due to excessive stimulation of the renal nerves, may be of pathogenic importance, inasmuch as it may temporarily increase renin production. But stress stimulates not only the nervous system, but also the CORTICOTROPHIN — and consequently the CORTICOID HORMONE — production. Thus it sets into effect another mechanism capable of causing renal-vascular damage and hence organic blood vessel constriction in the kidney. If the blood pressure is persistently increased by either of these mechanisms the renal blood supply may be sufficiently diminished to cause a great excess of renin production, especially in predisposed individuals

The rôle of ADRENALINE and VASOPRESSIN, in the spontaneous hypertension of man, is not yet known. There is no reason to doubt, however, that a prolonged rise in arterial pressure, occasioned by these hormones could also initiate the above-mentioned vicious circle. The discharge of these hormones is likewise under the controlling influence of the nervous system; this raises the possibility of their participation during the neurogenic phase of hypertension

Whatever the mechanism through which nephrosclerosis occurs, it is obvious that the accompanying arteriolar and glomerular damage decreases the blood supply of many glomeruli and hence, produces in these a condition similar to that which has been exper-

imentally induced in the entire kidney by constricting ligatures on the main arteries. Thus a vicious circle could be set up, since each of the affected nephrons would be transformed into "ENDOCRINE NEPHRONS," miniatures of the "endocrine kidney" produced by constriction of the main artery. This transformation could result in an increase in systemic blood pressure and could thus further aggravate the mechanical damage to the renal arterioles and consequently the nephrosclerosis.

CONSTRICTION OF THE MAIN RENAL ARTERY rarely plays a rôle in the pathogenesis of spontaneous hypertension in man. Only occasionally does an arteriosclerotic plaque, a scar or a tumor imitate the arterial clamps used in experimental medicine.

It is not definitely established whether renin plays an important part in the MAINTENANCE OF THE NORMAL BLOOD PRESSURE. It is noteworthy however that following hemorrhage, shock, etc., when the systemic blood pressure falls, renin production by the kidney is demonstrably increased. Presumably this is due to the participation of the kidney in the general systemic decline in intra-arterial pressure characteristic of shock. It is possible that operations selectively diminishing the blood supply to the kidney only, set into effect a homeostatic mechanism originally planned to maintain the arterial pressure at a normal level. If only the renal vessels are constricted, however, the intra-vascular pressure within the kidney is disproportionately low and this sets into action adaptive mechanisms designed to raise it towards normal. Under physiologic conditions the kidney "estimates" the amount of pressor substance necessary to maintain a normal systemic blood pressure, by the intra-vascular pressure within the renal parenchyme. This index becomes unreliable, however, in the presence of selective constriction of the renal arteries; hence an excess of pressor material is produced.

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HORMONES OF THE GASTROINTESTINAL TRACT

INTRODUCTION

The gastrointestinal tract elaborates a number of substances which regulate the functions of the digestive system. *It is of historic interest that the discovery* by Bayliss and Starling (1902) of one such principle "secretin" furnished the occasion to coin the term "hormone" for the group of "chemical messengers" to which this compound belongs.

The study of gastrointestinal hormones has not been pursued as actively as that of other branches of endocrinology perhaps because of the great inherent technical difficulties Unlike most of the typical endocrine organs, the *hormone* producing segments of the gastrointestinal tract have many other functions apart from their internal secretions; hence their surgical removal results in hormonal insufficiency symptoms complicated by other functional deficiencies.

Only a few of the gastrointestinal hormones have been isolated in chemically more or less pure form. The existence of numerous, separate, active principles of this type has been postulated but the physiologic rôle, and true hormonal nature of many among these is still in doubt.

It is curious that concomitantly with the morphologic specialization of certain tissues as endocrine glands, the actions of their hormonal principles also become more and more specific. The comparative non-specificity of the actions of gastrointestinal hormones (stimulation or inhibition of gastro-

intestinal secretions, contractions, etc.) adds to the difficulty of identifying them as special hormonal principles since many types of tissue extracts exhibit similar properties. (See also: pp. 9-12.)

SECRETIN

It has been noted that when acid gastric secretion or a solution of HCl enters the duodenum, a copious flow of pancreatic juice ensues. The same result is obtained by introducing HCl into a denervated loop of duodenum, which is completely isolated from the rest of the gastrointestinal tract and remains connected with the rest of the body only through its blood vessels. Complete denervation of the pancreas likewise fails to interfere with the stimulation of its secretion under such conditions. All these observations indicate that the duodenum influences pancreatic secretion through humoral means. The responsible principle, which was subsequently extracted from the duodenal mucosa, was termed "secretin."

Pure CRYSTALLINE PREPARATIONS of secretin picrolonate have been subsequently obtained (*Agren et al 1933-1937*) and it was found to be a polypeptide with a molecular weight of about 5000 When injected intravenously, it is extremely active in stimulating pancreatic secretion but exerts no significant effect upon the secretion of the stomach and the salivary glands; it causes only moderate intestinal and bile secretion and does not significantly alter the blood pressure or the blood sugar

Usually the gastric contents are sufficiently acid to elicit secretion production, and consequently pancreatic secretion, when they enter the duodenum, it is generally assumed therefore that secretin is a true hormone which plays a physiologic rôle in the regulation of digestive processes

The serum contains an enzyme "SECRETINASE," which rapidly destroys the hormone, this may explain the transitory nature of pancreatic secretion after injection of secretin and the absence of the hormone in urine.

VAGAL STIMULATION also increases pancreatic secretion, but the humoral mechanism appears to be more important than the nervous.

The intravenous injection of secretin proved useful as a FUNCTION TEST in the study of pancreatic secretion in man. The total amount of enzyme produced rises after secretin treatment and the secretion is increased in amount and in bicarbonate content, but its concentration is diminished.

Some investigators claim to have separated a special enzyme-secretion-stimulating factor "PANCREOZYMIN" from the crude secretin preparations; the fully purified secretin residue allegedly augments only the secretion of water and inorganic materials.

ENTEROGASTRONE

The ingestion of fat or sugar inhibits gastric secretion (*Ewald and Boas, 1886*) and delays the evacuation of the stomach, due to an inhibition of its motility. This effect does not originate in the stomach, but only in the duodenum when the food enters it. Even an autotransplanted denervated gastric pouch responds with an inhibition of secretion and motility following oral administration of fat or sugar. This inhibitory effect of nutrients is not due to absorption of the products of digestion but presumably to the formation of a hormone in the duodenal mucosa.

It has subsequently been demonstrated that duodenal extracts inhibit the secretion and contractions of the stomach normally elicited by fasting, histamine, insulin, or the ingestion of a normal or "sham" meal (that is a meal which is swallowed but immediately lost through an esophageal fistula).

It has not been possible to isolate enterogastrone but certain highly purified preparations were obtained which (given intravenously or subcutaneously) inhibit gastric motility and secretion, without exerting any effect upon the contractions of the gall bladder, the blood sugar level or pancreatic secretion. Indeed further purification of such extracts led some investigators (*Ivy et al.*) to suspect the existence of THREE DISTINCT PRINCIPLES in ordinary enterogastrone preparations . one which inhibits gastric secretion, a second which diminishes the motility of the stomach after vagotomy and a third which inhibits the motility of the normally innervated stomach Further work will be necessary to identify these supposedly distinct principles

It has been assumed that a deficiency in enterogastrone production may be responsible for certain types of gastric hyperacidity and of gastrointestinal ulcers. Preliminary experiments suggest that administration of enterogastrone counteracts the development of various experimental ulcers in animals and even of spontaneous peptic ulcers in man.

Enterogastrone is particularly effective in preventing the formation of peptic ulcers in dogs with a pyloro-jejunostomy in which the alkaline pancreatic juice and bile drain directly into the last 15 cm of the ileum, where the duodenum is transplanted. Normally, almost all dogs develop peptic ulcers after this so-called *Mann-Williamson operation*, unless they receive enterogastrone treatment Enterogastrone either increases the resistance of the jejunal mucosa to ulceration or promotes the repair and healing of ulcers.

UROGASTRONE

It has been noted that the urine of dogs and man contains a substance "urogastrone" which, like enterogastrone, inhibits gastric secretion and motility, its chemical structure and hormonal nature have not yet been established.

The substance allegedly originates from the duodenum and small intestine; its concentration in the urine increases after the ingestion of fat and diminishes following resection of the entire small intestine. Even in man injection of urogastrone diminishes gastric secretion under resting conditions as well as after the administration of histamine.

Unlike crude enterogastrone preparations, urogastrone does not inhibit gastric motility and it has therefore been assumed to be identical with that fraction of enterogastrone which merely impedes the secretion of the stomach without inhibiting its contractions.

It is debatable whether the pancreatic-secretion-inhibiting power of urogastrone preparations is due to a special principle "UROPANCREATONE"

ANTHELONE

The name "anthelone" ("anti" + "helicon" = ulcer) has been given to a fraction of the urine which prevents the Mann-Williamson ulcers in dogs by stimulating fibroblastic proliferation epithelialization and blood vessel formation in the gastric mucosa. It does not depress gastric secretion and thus differs from enterogastrone and urogastrone Very little is known about its possible physiologic significance and there is no proof that it is a true hormone

GASTRIN

It has been noted that the intravenous injection of acid extracts prepared from the gastric or duodenal mucosa (of dogs or man) stimulates the secretion of the stomach in the dog It was assumed that the substance responsible for this effect is a hormone of the stomach which received the name "gastrin" (*Edkins*, 1905-1906). The specificity of this effect has been contested, since various organ extracts can stim-

ulate gastric secretion and this is especially true of those which (like the stomach and duodenum) contain much histamine. It is particularly noteworthy that this action of organ extracts is inhibited by histaminase, an enzyme which selectively destroys histamine. Hence, probably the stimulation of gastric secretion by such organ extracts (as well as that obtained by the intravenous injection of gastric juice itself) depends upon their histamine content.

However, more recently, a preparation of pyloric mucosa was obtained which is extremely potent in stimulating the secretion of the fundic glands and contains neither histamine nor choline. Many of its chemical properties resemble those of secretin and its intravenous injection elicits the secretion in large quantities of a strongly acid gastric juice, which is practically devoid of pepsin. The pyloric mucosa is richest, that of the duodenum and especially that of the small intestine comparatively poor in this gastrin (*Komarov, 1938-41*) Histamine-free liver extracts also contain large amounts of gastrin-like material Allegedly such pure gastrin has no effect upon the secretion of bile or pancreatic juice and does not affect the blood pressure.

The existence of a true hormonal mechanism for the stimulation of gastric secretion by the gastric cells themselves is also supported by the following observations :

(1) If a dog with an autotransplanted gastric pouch is fed, the transplant is stimulated to secrete (*Ivy et al. 1925*). Presumably when the animal was fed, something entered its blood and stimulated the pouch.
(2) The mechanical or chemical stimulation of an isolated and denervated pyloric pouch, stimulates the secretion of a denervated gastric-fundus pouch in the same animal.
(3) Injection of blood, taken during the height of gastric secretion from one dog, induces secretion of the stomach in a second, receptor animal.

The greatest difficulty in this type of experimentation is to eliminate the possibility that absorption products enter the blood stream from the stomach and act as secretagogues upon gastric cells in other locations.

It is very probable that the original gastrin preparation of *Edkins* owed its secretagogue effects mainly to its histamine content, but the purified extracts appear to be devoid of such contamination. It is not impossible, however, that histamine itself also acts as a "gastric hormone" inasmuch as its increased discharge from the stomach-mucosa, in the early stages of digestion, could further augment the production of stomach juice.

Some investigators believe that the excessive chronic secretion of gastrin or histamine may be the cause of certain peptic ulcers in man.

DUODENIN

Certain duodenal extracts produce hypoglycemia in intact animals presumably due to a trophic action on the Langerhans' islets. However, some reduction of the hyperglycemia elicited by pancreatectomy has also been noted, so that the entire effect cannot be mediated by the pancreas. The hormonal nature of this "duodenin" (*Heller, 1931*) is in doubt.

INCRETIN

Some duodenal extracts produce hypoglycemia, following oral or intravenous administration, allegedly due to their stimulating effect upon the secretion of insulin by the pancreas. The effect is allegedly manifest even in human diabetes and has been attributed to a special principle . "incretin" (*La Barre, 1933*). The hormonal nature of incretin is in doubt; it may be identical with the above-mentioned duodenin.

OTHER BLOOD-SUGAR-DEPRESSING DUODENAL EXTRACTS

Several other more or less purified duodenal extracts (e.g., "DUOCRINE") have been claimed to contain specific blood-sugar-influencing hormones, some of which act only in the presence of the pancreas and presumably exert their effects through the stimulation of islet cells. It is noteworthy that impure secretin preparations also cause hypoglycemia, but this is not the case if the active principle is sufficiently purified.

It is highly dubious whether the duodenum produces any true hormonal substance which influences the blood sugar level; if such exists, it is not identical with secretin.

VILLIKININ

It has been found that the introduction of acid into an intestinal loop strongly stimulates the movements of the intestinal villi. Acid extraction of intestinal mucosa yields a substance "villikinin" which is allegedly responsible for this activity (*Kokas and Ludány*, 1933-36). Purified villikinin preparations are devoid of histamine, adenosine, choline and secretin. The hormonal nature of this effect has not yet been confirmed.

ENTEROCRININ

If intestinal juice is injected subcutaneously there is an increase in intestinal secretion, without any change in the production of bile, saliva, gastric or pancreatic secretion (*Frouin*, 1904-05).

This activity has been ascribed to a hormone liberated during intestinal digestion Further evidence in favor of this hypothesis is that the secretion of intestinal juice is demonstrably augmented during digestion, even in an isolated intestinal loop and, if acid is introduced (through a fistula) into such an isolated intestinal segment other isolated intestinal loops in the same animal also begin to secrete.

Nasset (1938) succeeded in preparing an extract from the intestinal mucosa, which selectively stimulates the secretion of the glands in the small intestine; he named the active principle "enterocrinin". It demonstrably differs from secretin, enterogastrone, and duodenin but its hormonal nature is far from being proven.

CHOLECYSTOKININ

Intravenous injection of certain intestinal-mucosa extracts cause contraction and evacuation of the gall bladder in animals (*Ivy and Oldberg*, 1928). The existence of a gall-bladder-contracting hormone has received further support from cross-circulation experiments. Introduction of acid into the duodenum of one dog elicits gall-bladder contractions in a second animal, connected with the first only through the blood vessel system. Even in man, transfusion of blood taken at the peak of digestion, causes gall-bladder contraction in a second individual; thus the humoral stimulation of gall-bladder contraction appears to be well established although it may be debated whether the active substance is a true hormone In any event it is present in extracts of the upper-intestinal mucosa, even if secretin and most other known possible contaminants are removed Only carbohydrate meals appear not to cause the production of this cholecystokinin Egg yolk and cream are most potent.

Clinical experience teaches us that during pregnancy the gall bladder does not empty well in women. In this connection it is interesting that in the guinea pig, the gall bladder is less responsive to cholecystokinin during gestation than otherwise Folliculoids likewise diminish responsiveness to cholecystokinin, even in spayed females.

Serum contains an enzyme which inactivates cholecystokinin.

HORMONES OF THE SALIVARY GLANDS

Saline extracts of resting submaxillary glands exert no effect upon the secretion of saliva when added to the perfusion fluid of another salivary gland. However, marked secretion is obtained under similar conditions with saliva and with extracts prepared from the submaxillary gland during hyperactivity elicited by stimulation of its nerve, the chorda tympani (*Demoor*, 1911-1913). It was concluded that the secretory impulse can be propagated through humoral means. The underlying principle, the "Chordastoff", has not been isolated, but it is claimed to be identical with acetylcholine, or some other choline ester; atropine abolishes its effect (*Henderson and Roepke*, 1933).

Probably the salivary-secretion-stimulating action of the substances produced under the influence of nervous stimulation is merely a neurohumoral transmission effect which acts locally. In the concentrations in which these substances would appear in the blood they are not likely to be effective at a distance.

The numerous publications concerning hypoglycemic and other metabolic hormones supposedly produced by the salivary glands are not yet adequately supported to deserve discussion here.

OTHER GASTROINTESTINAL HORMONES

There is no definite evidence for the production of any other hormonal principle by the gastrointestinal tract and even the identity of many among those mentioned above is by no means proven.

For participation of the stomach in the production of anti-anemic substances (intrinsic factor) see: p 794

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BABKIN, B. P.: *Secretory mechanism of the digestive glands.* Paul B. Hoeber, Inc. Publ. New York (1944.)

A book (900 pages, 220 illustrations, more than 1,500 references) in which an extensive section (86 pages) is devoted to an excellent review of the gastrointestinal hormones.

GREENGARD, N. *Hormones of the Gastrointestinal Tract.* In: The Hormones. Pincus. G and K. V. Thimann (Ed). Academic Press Inc., Publ, New York (1948).

A review (53 pages, 4 figures, 361 references) concerning recent advances in the study of gastrointestinal hormones.

HOUSSAY, B A · *Hormonas del aparato digestivo.* Aniceto Lopez, Publ, Buenos-Aires (1944)

A review (16 pages, 5 illustrations, few references) in which the present day status of the hormones of the gastrointestinal tract is critically reviewed (In Spanish)

IVY, A C. · *The gastrointestinal hormones, their physiology and applications* Tr. & Stud. Coll Physicians, Philadelphia 12, 101 (1944)

A review (7 pages, no illustrations, 47 references) mainly based on the author's extensive personal experience with the hormones of the gastrointestinal tract.

CARDIAC HORMONES

It has been observed that certain heart extracts stimulate the amplitude and intensity of the cardiac contractions in vitro (*Haberlandt*, 1924.) This action has been attributed to a special heart hormone or "Herzhormon" It is highly probable that various non-specific tissue constituents (adenosine, adenylic acid, etc.) are responsible for this action, which is not by any means proven to be of hormonal nature.

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DEPRESSOR SUBSTANCES OF TISSUES

Many tissue constituents are known to possess depressor, vasodilator properties. It is doubtful whether they should be ascribed to true hormones but it has been shown that several of these substances can influence blood vessels at a distance from the site of their formation and thus act like "chemical messengers"; hence their discussion here appears to be justified.

HISTAMINE

Among the vasodilator substances of tissues, histamine is especially important. It is present in many organs and can be FORMED in vitro by the decarboxylating action of bacteria upon the amino-acid histidine. It is probably in this manner that histamine is formed in the intestine.

The DISTRIBUTION of histamine among the organs differs in the various animal species. In the omnivora (e g., dog) the liver and intestinal tract; in the guinea pig, the lung contains especially large amounts. Human blood contains about 1-8γ/100 cc., most of it being in the leucocytes and especially in the eosinophiles.

Histamine has extraordinarily pronounced pharmacologic effects. Upon intravenous administration 0.1γ suffices to produce a marked fall in BLOOD PRESSURE in ether-anesthetized cats. 1γ produces severe hypotension, even in the human being. Anesthesia increases susceptibility to histamine Both arterioles and capillaries are dilated under its influence but the relative effects upon specific vascular territories varies according to the animal species under consideration.

The MUSCULOTROPIC ACTIONS of histamine are so marked that some of them serve as a basis for its bioassay (e g., contraction of guinea pig intestine or uterus in vitro) It is due to this musculotropic effect upon the bronchioles, that histamine produces emphysema and asthma (e g., guinea pig, man).

Histamine also stimulates the copious SECRETION OF VERY ACID GASTRIC JUICE. in man 0.25/0.5 mg. subcutaneously produce a marked response of this type.

It is especially noteworthy that during ANAPHYLACTIC AND PEPTONE SHOCK large amounts of histamine are discharged from the liver (dog), or lung (guinea pig) and many investigators believe that histamine intoxication is the ultimate cause of anaphylactic phenomena.

During SHOCK due to intensive injury to tissues (mechanical, toxic, thermal) presumably large quantities of histamine are also discharged from the cell-bodies of the damaged tissues and some investigators believe that this may play an important part in the ALARM REACTION According to one interpretation, histamine occurs in the cells as an inactive protein-conjugate from which active histamine is liberated during shock, under the influence of specific enzymes

HISTAMINASE is an enzyme, which destroys histamine. It is particularly plentiful in kidney and intestine. Its physiologic significance has still not been clarified, it does not significantly alter the pharmacologic effects of histamine in vivo.

Recently, various ANTI-HISTAMINE DRUGS (e g. benadryl) have been found, which antagonize the actions of histamine (except its effect on the stomach) and are useful in the treatment of allergic conditions presumed to result from endogenous histamine intoxication

ACETYLCHOLINE

As previously stated, in connection with the theory of sympathin (see: Adrenals) acetylcholine is liberated at

postganglionic parasympathetic nerve endings as well as at the preganglionic endings of both parasympathetic and thoracic sympathetic fibers. It is the acetic acid ester of the alcohol choline: the latter is plentiful in various tissues since it is a constituent of lecithin and sphingomyelin. Free choline is a comparatively inert vasodilator, but acetylation raises its activity at least a thousand times Normally only traces of free choline are present in the body. It acts upon blood vessels essentially in the same manner as acetylcholine, although quantitatively its effect is much inferior.

Acetylcholine closely imitates all the effects of parasympathetic stimulation: it causes cardiac inhibition, stimulation of smooth-muscle contraction in the gastrointestinal tract and urinary bladder, secretion of saliva, tears and sweat, dilatation of the arterioles and a consequent fall in blood pressure Its potency is so great that some of its pharmacodynamic actions (e.g., inhibition of perfused frog's heart, contraction of isolated intestinal segment) are exhibited at concentrations of one part in many millions.

CHOLINESTERASE is an enzyme which greatly accelerates the hydrolysis of acetylcholine in alkaline media. The resulting choline — separated from the acetyl group — is so much less active that this hydrolysis is tantamount to a pharmacologic inactivation *Physostigmine* (eserine) inhibits this action of cholinesterase and by thus protecting acetylcholine augments its pharmacodynamic effects.

DIISOPROPYL-FLUORO-PHOSPHATE (DFP) is a compound with somewhat related acetylcholine-protecting actions

It is customary to subdivide the actions of acetylcholine into "nicotine-like" and "muscarine-like" effects The "*nicotine-like*" actions are, stimulation of: ganglion cells, voluntary frog muscle, denervated mammalian muscle and the muscles of the body-wall of the leech. None of these actions, which acetylcholine has in common with nicotine, are abolished by atropine, but they can be inhibited by curarine or very large doses of nicotine.

The "*muscarine-like*" actions of acetylcholine are its typical parasympatheticomimetic effects: these are abolished by atropine and resemble those of parasympathetic nerve stimulation. Atropine presumably acts directly upon the effector cells preventing the effectiveness, but not the actual production, of acetylcholine.

The important rôle of acetylcholine, in the humoral *transmission of nervous stimuli*, has mainly been established on the basis of experiments essentially similar to those mentioned in connection with sympathin (see: p. 114) Following stimulation of parasympathetic nerves, large quantities of a substance with acetylcholine-like properties appear in the venous blood of the organ whose nerves are stimulated It has been shown in this manner that acetylcholine is liberated upon stimulation of the chorda tympani (which stimulates secretion of the salivary glands), the parasympathetic nerves of blood vessels (vasodilators), those of the iris (here acetylcholine appears in the aqueous humor), the alimentary tract in vitro (here acetylcholine becomes demonstrable in the suspension fluid), the urinary bladder, preganglionic sympathetic nerve endings (e.g., acetylcholine appears in perfused, eserinized, superior cervical ganglia during stimulation of the cervical sympathetic trunk), etc. Indeed, since even the sympathetic fibers which stimulate adrenaline production in the adrenal medulla correspond to preganglionic sympathetic nerves, acetylcholine liberation is the adequate stimulus to initiate adrenaline discharge. The transmission of the secretory stimulus to sweat glands is also mediated by acetylcholine (demonstrable in the eserin-

ized perfusion fluid) although these structures are innervated by (anatomically) sympathetic fibers. (See: p. 115)

It is also highly probable that the chemical transmission of motor nerve impulses to voluntary muscles is mediated by acetylcholine. We have already mentioned (see: p. 107) that denervation increases the sensitivity of the effector organs to adrenaline and sympathin. The same is true of their acetylcholine sensitivity in agreement with Cannon's *law of denervation* which states: "When in a series of efferent neurons a unit is destroyed, increased irritability to chemical agents develops in the isolated structure or structures, the effect being maximal in the part directly denervated."

An interesting application of this law of denervation is the so-called *"fright reaction,"* which consists in the involuntary contraction of the facial muscles observed in monkeys whose 7th cranial nerve has been severed. Fright liberates sufficient acetylcholine (from unknown sources) to effect a contraction of these voluntary muscles, after sensitization by denervation. Injection of acetylcholine into such animals provokes essentially similar responses.

It will be noted that *acetylcholine enters the blood stream* and can specifically affect organs at a distance from the site of its origin, as classic hormones do. This however, is not its usual mechanism of action. In order to demonstrate such blood-borne effects it is necessary to sensitize the organism e.g., by drugs or denervation. Under physiologic conditions the main effects of acetylcholine — unlike those of hormones — are locally exerted at the nerve endings where the substance is liberated.

Both of the great integrating systems of the organism — the endocrine and the nervous system — can selectively influence a variety of organs for the purposeful coordination of their actions. The classic hormones, which are discharged into the general circulation, can achieve this selective organotropism only by the great variety of their chemical structure; conversely, two comparatively simple chemical substances, acetylcholine and sympathin (the latter perhaps identical with adrenaline), suffice for the humoral mediation of the manifold effects of nerve stimulation. This is so merely because they can be liberated with great selectivity at the very site at which they are to exert their actions. If sympathin and adrenaline should prove to be identical — as many authors think they are — then the hormone of the adrenal medulla would assume a somewhat intermediary position inasmuch as it could either cause general effects, following liberation into the blood stream from the adrenal medulla, or highly selective but entirely localized effects, upon liberation from sympathetic nerve endings.

KALLIKREIN

Kraut and Frey (1934) isolated a vasodilator substance from normal human urine which presumably differs from all other known vasodilators. It was named "kallikrein" and commercial preparations of it bore the trade-designation "padutin."

Upon intravenous injection it causes a fall in blood pressure, tachycardia and an increase in the amplitude of the pulse. It differs from histamine in that (1) it does not produce constriction of the bronchioles in the guinea pig, (2) it lowers the blood pressure of the rabbit, while histamine is ineffective in this respect when ordinary anesthetics are used. Its hypotensive effect — unlike that of acetylcholine — is not inhibited by atropine. The substance is rapidly inactivated by serum, but can be reactivated by the addition of acid.

It has been claimed that kallikrein is a pancreatic hormone, since the pan-

creas is very rich in it; however, its origin has not been proven. When, as a result of great metabolic activity, the tissues become acid, kallikrein is allegedly liberated from them and then causes vasodilatation.

ANGIOXYL

Angioxyl is the name given by *Gley and Kisthinios* (1929) to a vasodepressor substance likewise isolated from the pancreas. It may well be identical with kallikrein.

VAGOTONIN

Santenoise et al. (1930) prepared a vagus-stimulating and hence depressor principle from the pancreas, or from comparatively crude insulin preparations. This substance "vagotonin" also possesses characteristic hypoglycemic properties and has already been mentioned in the chapter on the pancreas. Its true hormonal nature has not been proven.

ADENOSINE AND DERIVATIVES

Adenosine and its derivatives such as adenylic acid are not very active vasodilators, but they may be present in tissues in pharmacodynamically important amounts. *Drury and Szent-Györgyi* (1929) found that the active depressor constituent of certain vasodilator skeletal and heart-muscle extracts was adenosine. The depressor effect is mainly exerted through a relaxation of the arterioles. Adenosine also causes a heart-block, which is characteristically inhibited by barium. Upon subcutaneous injection — unlike histamine — adenosine has leucotactic properties, that is, it attracts leucocytes. Its physiologic rôle is not known but it can hardly be regarded as a hormone.

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HEPATIC HORMONES

THE ANTIANEMIC PRINCIPLE

Pernicious Anemia. — *Addison* (1849) was the first to recognize this disease as one of the anemias. About 20 years later *Biermer* named it "pernicious anemia" and gave an excellent description of this malady which is therefore sometimes referred to as Addison-Biermer's disease.

Pernicious anemia is essentially due to defective erythrocyte formation. Presumably the early large forms of the red cells (megaloblasts) multiply but fail to mature so that they remain unusually large (8.25-9μ) as compared to the normal (7.5μ).

The MAIN CHARACTERISTICS of pernicious anemia are

(1) *Marked reduction in the number of erythrocytes.* In severe cases the blood count may only be 10% of the normal.
(2) *High color index* The hemoglobin and iron content are less markedly reduced than the number of red cells.
(3) *Megalocytosis* (megalocytes are red blood cells whose diameter is 12-25μ)
(4) *Poikilocytosis and anisocytosis* (great variation in the shape and size of the erythrocytes)
(5) *Leukopenia* with a reduction of the total number of leucocytes but *a relative increase in the lymphocyte count.*
(6) *Rise in plasma iron and bilirubin* with increased excretion of urobilin in stools and urine.
(7) *Reduction in blood platelets.*
(8) *Deposition of hemosiderin in tissues* (e g., liver, spleen, kidney).
(9) *Reduced fragility of the erythrocytes*
(10) *Replacement* (especially in the long bones) *of fatty by red bone marrow rich in megaloblasts.*
(11) *Achylia gastrica* associated with an atrophy of the mucosa of the stomach and lack of both pepsin and HCl in the gastric secretion. Frequently achylia exists many years before the other signs develop. Pernicious anemia is invariably associated with this derangement in gastric secretion although, many patients with achylia gastrica never develop pernicious anemia.
(12) *Glossitis* with more or less severe pain in the tongue.
(13) *Lesions in the central nervous system,* usually primary degeneration of the myelin sheath in the posterior columns and pyramidal tracts, without glia reaction.
(14) *Remissions and relapses.* During remissions the blood picture may become almost normal after a so-called "blood crisis" in which the percentage of reticulocytes increases.

The Antianemic Factor of Liver. — *Whipple et al* (1925) found that in dogs, rendered anemic by repeated bleeding, feeding of beef liver helps blood regeneration. Stimulated by

this observation *Minot and Murphy* (1926) successfully treated patients suffering from pernicious anemia with liver given by mouth. About 400 gm./day of raw, or lightly cooked, liver was necessary, while using the highly purified liver extracts now available, 1 mg. per day suffices. The active principle has been termed "antianemic" or "hematinic principle": it is contained in the non-protein fraction of the liver and can be given by mouth, although intramuscularly it is about 30 times more active.

Unlike normal human liver, that of untreated patients with pernicious anemia does not contain the antianemic principle, unless liver therapy is instituted.

Folic Acid. — It has long been suspected that hepatic tissue contains at least one other hemopoietic substance which is related to the vitamin-B complex. Recently it was found that folic acid (from the latin "folium" = leaf) which may belong to the vitamin-B complex, is highly effective in many cases of pernicious and other types of anemia, including some which are refractory to liver therapy. About 10 mg./day are required either enterally or parenterally Liver, kidney, mushrooms, yeast and the green leaves of many plants (e.g., spinach, grass) contain large amounts of folic acid. This substance has been isolated in pure form and can be synthesized in vitro, it has been given the chemical name "pteroylglutamic acid." In addition to its antianemic properties it stimulates the growth of mammals (e g . rat) and of certain bacteria (e.g., lactobacillus casei).

Folic acid is not identical with the antianemic principle of the liver, since highly active hepatic extracts contain only traces of it, nor can it be the "extrinsic factor" of Castle (see below) since, unlike the latter, it is not activated by incubation with normal gastric juice. The exact relationship of folic acid to the hepatic and gastric antianemic substances is not yet clear.

The Antianemic Principle of the Stomach. — *Castle* (1929) found that if the gastric contents of a normal person are removed during the digestion of meat and fed to a patient with pernicious anemia, the same type of curative effect is obtained as if liver were fed. Gastric juice itself (e.g., that obtained by histamine injection) is ineffective, but if it is incubated with meat (e.g., beefsteak) an active principle is obtained in vitro. Pepsin, rennin, lipase, HCl as well as gastric juice from patients with pernicious anemia, proved ineffective in activating meat in vitro. In normal gastric secretion however, there is a special enzyme-like substance which, unlike pepsin (optimal pH 1.6), acts best at pH 7 and forms the antianemic factor from meat This was termed the "INTRINSIC FACTOR." Desiccated and defatted pig stomach is rich in this intrinsic factor and can be given by mouth, instead of the liver extract, to patients with pernicious anemia.

In man, the fundus of the stomach appears to be its source; accordingly, patients with pernicious anemia usually display a severe atrophy of the fundic mucosa with destruction of the gastric glands. In patients with achlorhydria, who do not suffer from pernicious anemia it is assumed that the formation of the enzyme-like substance is not, or not yet, impeded.

According to the most generally accepted theory the enzyme-like "intrinsic" factor acts upon a dietary precursor (present in meat, yeast, etc.) the so-called "EXTRINSIC FACTOR" to form the antianemic principle within the lumen of the stomach. The activated antianemic factor is then carried to the liver merely for storage. When needed it is released from the hepatic cells and then it directly stimulates the bone mar-

row to produce normal erythrocytes In pernicious anemia the gastric mucosa fails to produce intrinsic factor and hence no antianemic principle is produced; therefore either activated stomach contents, or hepatic extracts containing the antianemic factor, must be given to permit normal erythropoiesis

Since normal gastric juice can activate autolyzed yeast (which is rich in vitamin B_2) it has been postulated that the extrinsic factor is vitamin B_2 or some closely allied substance, but other materials rich in vitamin B_2 are not activated by gastric juice, so that this view is hardly tenable

In agreement with the above interpretation, pernicious anemia could, at least theoretically, result from (1) lack of intrinsic-factor production by the stomach, (2) lack of extrinsic factor in the diet, (3) deficient absorption of the activated antianemic principle from the intestine, (4) inability of the liver to store the antianemic factor, (5) an irresponsiveness of the hematopoietic tissue to the antianemic principle.

In the most common type of *pernicious anemia* the elaboration of the intrinsic factor appears to be at fault, in the anemia of *sprue* the absorption and in severe *hepatic disease*, the storage of the antianemic factor are probably deficient A special (very rare) *type of pernicious anemia, which is resistent to treatment with active hepatic extracts* is apparently due to the inability of the bone marrow to utilize this principle

Some investigators refer to the antianemic principle of the liver as a hormone It is doubtful however, whether the term is applicable in this case since the active principle is not elaborated in a cell but within the lumen of the stomach and is merely stored by hepatic cells It appears equally inadmissible to regard the intrinsic factor as a hormone, since it is not discharged directly into the blood stream but into the gastric contents.

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HEPARIN

It has long been known that extracts of liver tissue inhibit blood-coagulation (*McLean*, 1916). The active principle "heparin" has also been prepared from lung, muscle and intestinal wall; it is now available in pure crystalline form. Some authors claim that heparin is inactivated in the body by a special enzyme *"heparinase"* Apparently heparin exerts its most important physiologic action as a local anticoagulant, which prevents blood clotting (due to its thrombin and prothrombin inactivating power) in specific vascular territories. This localization of action is possible because heparin is probably elaborated by the mast cells — the wandering basophiles of tissues — which tend to accumulate around the small blood vessels of tissues containing much heparin

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YAKRITON

Sato and his co-workers (1926-1940) believe that the well known detoxifying function of the liver is, at least partly, due to a special detoxify-

ing hormone, which they named "yakriton." These authors claim to have extracted a substance from hepatic tissue, which, when given to animals simultaneously with a variety of toxic substances (e.g., histamine, urea, ammonia, chloralhydrate) augments drug-resistance.

A good deal of evidence has accumulated in support of the view that certain hepatic extracts have detoxifying effects, but it has not been proven that this is due to hormones.

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HORMONES IN INVERTEBRATES

Even invertebrates appear to produce hormone-like substances. Thus it was shown that in certain insects removal of specific cell-groups (e.g., the corpora allata) causes definite deficiency symptoms, which can be corrected by an extract of the tissue removed. Thus the so-called "CORPUS ALLATUM HORMONE" was found to be necessary during metamorphosis in Orthoptera; the diurnal pigment-migration in the eyes of certain crayfish, proved to be controlled by an endocrine organ, the sinus gland, through a special "EYE-STALK HORMONE," etc.

There is no reason to doubt the true hormonal nature of such factors, but their discussion is beyond the scope of this book.

The hormones of vertebrates are remarkably ineffective in influencing the development of invertebrata, although ACETYLCHOLINE and ADRENALINE appear to play their usual rôle in the transmission of nervous impulses even among these lower animals.

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PLANT HORMONES

A number of substances have been isolated from urine, or synthetized in vitro, which selectively influence morphogenesis and certain physiologic functions in plants (e.g., growth, geotropism, root formation, development of lateral buds and shoots, flowering). These are sometimes referred to as "plant-hormones", "auxins" or "phytohormones." Chemically, they are diverse derivatives of indole, naphthyl, etc.

Some auxins are normally produced by plant cells and can be regarded as true hormones with a physiologic rôle in the plant kingdom. They assume an increasing importance in agriculture since they are useful in promoting the growth and fruit formation of plants

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HUMORAL FACTORS IN INFLAMMATION AND WOUND HEALING

During the last ten years it became obvious, mainly as a result of *Menkin's* investigations (1936-1947), that the development of an acute inflammatory reaction, the localization of the irritant, its final disposal, and the consequent wound healing, are under the influence of humoral agents. Since the action of these substances is not strictly physiologic, and is mainly limited to the site of irritation, they can hardly be regarded as true hormones Hence we shall merely mention them here

(1) LEUCOTAXINE, a nitrogenous product present in inflammatory exudates, which has allegedly been crystallized and is probably a polypeptide. It augments phagocytosis, capillary permeability and the diapedesis of polymorphonuclear leucocytes.

(2) A LEUCOCYTOSIS-PROMOTING FACTOR (L P F.) increases the number of leucocytes in the circulating blood, it also stimulates the growth of granulocytes and of megakaryocytes in the bone marrow

(3) NECROSIN, a toxic factor in the euglobulin fraction of inflammatory exudates, exerts a pronounced proteolytic activity and causes local necrosis.

(4) PYREXIN, a substance in exudative material, which causes fever.

(5) A LEUCOPENIC FACTOR, also present in the euglobulin fraction of inflammatory exudates, is supposedly responsible for the leucopenia associated with certain types of inflammation.

(6) GROWTH-PROMOTING FACTORS stimulate wound healing and repair.

All these substances are allegedly liberated from cells under the influence of irritants and play an important rôle in the process of inflammation. They are claimed to differ from histamine, the so-called "H-factor" of Lewis, acetylcholine, adenine compounds, hyaluronidase, and all other metabolites previously described as being discharged from the bodies of decomposing cells. Their chemical nature and biologic function has not been fully clarified.

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A brief summary (3 pages) concerning the author's investigations on humoral factors in the process of inflammation and regeneration Only the most important key references are cited.

XII

CORRELATIONS

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HIBERNATION AND AESTIVATION

Hibernation. — Hibernation is a coma-like condition which develops in certain animals, during the winter season, under the influence of cold and lack of food. Many invertebrates, amphibia, reptiles and some (exceptional) fish, spend the winter in a condition of immobility, during which their metabolism falls to very low levels. It is only in this manner that they can resist the hardships of the cold season.

The term hibernation or "winter-sleep" is more commonly used, however, for a similar condition, which affects a limited number of mammalian species (e.g., gopher, chipmunk, ground-squirrel, hedgehog, bat, dormouse, marmot). It is customary to speak of hibernation in the bear, but in this species the body temperature remains essentially normal, although the animal falls into a condition of rest and torpor during the winter season

During typical winter-sleep the hibernating animal usually retires into some protected hiding place, such as a cave or a hole in a tree, where it curls up (to decrease its body surface and hence its loss of heat) and becomes comatose. All other vital processes decrease considerably, thus the BODY TEMPERATURE may fall in the urchin to +15° C. and in certain bats even below 0° C In the urchin the RESPIRATION rate, which is normally about 50/min., falls to about 1/min., while the PULSE rate decreases from the normal of 300/min. to 2-3/min.

The R.Q. falls to about 0.50 because these animals generally accumulate a large amount of body fat before hibernation and then, during the winter season, they live almost exclusively on this FAT (to a lesser extent on protein), while the CARBOHYDRATE reserves (e.g., glycogen) remain practically intact and marked hypoglycemia develops. At the same time the total BODY WEIGHT diminishes enormously, since during the entire winter season the hibernating animal consumes almost no food.

It has long been suspected that hibernation is influenced by the endocrines. The ANTERIOR-HYPOPHYSIS, THYROID, GONAD and ADRENAL (medulla and cortex) undergo severe atrophy, while the adrenaline and ascorbic acid content of the adrenals fall to very low levels in most hibernating animals. The development of the pancreatic LANGERHANS ISLETS, however, appears to be stimulated. In the TESTIS, spermatogenesis usually ceases although the Leydig cells may be well (or even excessively) developed. In certain bats copulation occurs in the Autumn and the sperm remains viable in the uterus of the female during hibernation, but ovulation and insemination occur only the following Spring after awakening from the winter-sleep.

Many observations indicate that injection of ADRENALINE or THYROXIN can arouse mammals from hibernation, while INSULIN treatment may induce a condition of winter-sleep especially if it is combined with exposure to cold. Curiously, the BLOOD-MAGNESIUM content, which rises in hibernating animals (e g., urchin) during the winter season, may be caused to rise at any time in the off-season, if a winter-sleep-like condition is induced by insulin.

It has been claimed that the awakening of animals with thyroid treatment is non-specific since injection of warm

physiologic saline (often used as a carrier of the thyroid hormone) in itself suffices to produce the same result. It is true that intravenous administration of much warm physiologic saline can arouse animals from hibernation, but adequate control experiments proved that the action of the hormones is specific and not merely due to the solvent in which they were given.

Since atropine may also interrupt hibernation it has been assumed that the PARASYMPATHETIC NERVOUS SYSTEM plays an important rôle but the exact mechanism through which humoral and nervous factors govern the winter-sleep has not yet been clarified.

Aestivation. — This is a condition essentially similar to hibernation: it is seen in certain lower animals during periods of extreme heat or drought in the summer. The possible rôle of humoral factors in aestivation has not yet been examined.

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PUBERTY, MENARCHE, ADOLESCENCE

DEFINITION

PUBERTY, in either sex, is the time at which reproduction becomes possible.

The term MENARCHE refers to the first menstrual bleeding, which is not necessarily ovulatory.

The term ADOLESCENCE designates the whole period of growth during which sexual differentiation occurs in girls and boys This is a gradual process which may extend over several years, since the maturation of the sex organs from the infantile to the adult condition proceeds slowly

COURSE

State. — The average AGE of puberty varies according to race, nutrition and other factors, but in the United States and Canada it is estimated to be about 14 years for females and 17 years for males At that time, the first potentially fertile ovulations occur in women and the first mature sperm cells are produced in men However, indications of somatic and psychologic sexual maturation are evident many years earlier.

In girls the menarche (which is only one of many prerequisites of fertility) is generally recognized as an objective indicator of the onset of puberty. In boys, the transition is more gradual and unaccompanied by any clear-cut indication of a turning-point. Theoretically, the first appearance of an ejaculate with mature spermatozoa could be considered as equivalent to the first ovulatory menstruation of girls.

In dating the onset of puberty, it must also be kept in mind that individual variations are great and the menarche should not be considered precocious or delayed unless it occurs under 9, or after 17 years of age respectively.

Since the first few menstrual cycles are frequently anovulatory and sometimes not preceded by progestational proliferation of the endometrium, even the appearance of bleeding is not a certain sign of puberty in the strict sense of the word.

Growth and Bone Changes. — About one year before the onset of the menarche, there is a sudden increase in somatic growth, so that at the time of their first menstruation, girls are usually taller than the average for that same age group. Following this period of "maximum rate of growth" *(Boas)*, there is a rapid decrease in the somatic growth rate, which almost comes to a standstill 1-3 years later. The earlier the menarche, the more rapidly growth in length ceases, hence women who begin to menstruate very early tend to have short statures when they reach adulthood.

Secondary Sexual Characteristics. — Until about 7 years of age the body contours of boys and girls are essentially similar but after this the sexual differentiation begins to manifest itself (adolescent period). The rounding of the female figure, with the widening of the pelvis and the enlargement of the BREASTS begin to distinguish the female figure from the male. The growth of AXILLARY AND PUBIC HAIR is also characteristic of the adolescent period. The upper border of the pubic hair zone is usually horizontal in females, while in males, it tends to have a triangular extension towards the umbilicus. However, many deviations from this typical pattern occur.

The VULVA enlarges, especially because of the marked development of the labia majora, which, in childhood, are practically non-existent so that the more prominent labia minora protrude. The CLITORIS becomes erectile Bartholin's glands begin to secrete The reaction of the vaginal secretion becomes increasingly more acid and Doderlein's bacilli appear in the vaginal flora The vaginal mucosa consists only of a few layers of stratified epithelial cells in children, but grows considerably in thickness. With the onset of the menses it also begins to undergo the well-known cyclic variations in its histologic pattern. (See: pp. 364, 366, 395.)

The UTERUS enlarges at the time of puberty, mainly due to an increase in the size of the corpus. The infantile cervix is less markedly influenced since it is proportionally larger than the corpus during the prepubertal period. The endometrium begins to show the characteristic cyclic variations. (See: pp. 362, 367, 394.)

The OVIDUCTS become larger and more convoluted.

The OVARIES increase in size and reveal the characteristic cyclic variations of follicle formation and luteinization. Ovulation may not occur during the first few uterine cycles. (See: pp. 382, 384.) Further maturation of the genitalia continues after the menarche. Hence, complete fertility is usually not attained until the 16th to 19th year.

The male ACCESSORY ORGANS exhibit a comparable enlargement during the puberty period. The penis, prostate and seminal vesicles undergo maturation; there is beard and mustache growth, with a marked increase in hair growth on arms, back, chest and thighs and the male type of pubic hair line develops.

Changes in the VOICE are much more conspicuous and sudden in boys, but definite alterations also take place in girls, although, here, they are so slight and gradual that they usually pass unnoticed. It is very probable that the effect of testoids upon the development of the larynx are responsible for the puberal change in voice in both sexes.

Among the PSYCHOLOGIC CHANGES, the development of sex-consciousness is most important Furthermore, many girls find the experience of the first menstrual bleeding particularly alarming but are ashamed to tell anyone about it Psychologic maladjustments

tend to be aggravated and prolonged during this critical period by the tendency of some mothers to impede the assumption of the adult status of puberal girls in the family. Complete psychosexual maturity is usually the last development It may not be attained until the early twenties.

It is important to explain the significance and hygiene of menstruation to puberal girls and to make them realize that normal menses do not materially interfere with their well-being. If a young girl is handled like an invalid during her menses and is made to believe that women are "unwell" at the time of their periods, one only increases the psychic trauma of this event and predisposes the child to the psychogenic type of primary dysmenorrhea.

FACTORS INFLUENCING THE DEVELOPMENT OF PUBERTY

RACIAL and perhaps also CLIMATIC factors exert an influence upon the onset of puberty. Thus, Southern races tend to mature earlier than the people of the North, although the importance of climatic factors is generally overrated

HEREDITY is certainly a most important factor, since in certain families, puberty is attained much earlier than in others.

It has been said that PSYCHIC FACTORS also exert an influence inasmuch as an atmosphere of sexual promiscuity (e g, in certain urban communities and savage tribes) allegedly promotes an earlier maturation than would be expected in a sheltered environment. However, there appears to be no very definite proof for this assumption

NON-SPECIFIC DAMAGE of any sort, such as malnutrition, chronic diseases, especially anemia, diabetes and tuberculosis, tend to delay the onset of puberty This phenomenon, as the previously mentioned amenorrhea due to non-specific damage in adults (see Ovarian Diseases in General) is probably due to the diminution of gonadotrophin secretion during the general-adaptation-syndrome, elicited by such noxious factors.

MECHANISM AND SIGNIFICANCE OF PUBERTY

The phenomena of puberty are due to an increase in the gonadotrophin secretion of the anterior-lobe. This causes maturation of the gonads, with increased secretion of gonadal hormones (folliculoids and luteoids in the female, testoids in the male) and these in turn affect the accessory sex organs as well as somatic and psychic development in general

Gonadotrophic and gonadal hormone production is by no means absent before puberty. Hypophysectomy in prepubertal animals causes involution of the ovaries or testes below their normal immature level; gonadectomy results in some degree of accessory-sex-organ involution in either sex, even when performed before the onset of puberty We do not know, however, what initiates the sudden increase in gonadotrophin production at the beginning of adolescence.

DISEASES OF THE PUBERTY PERIOD

Among the diseases of the puberty period, the most important are puberty hemorrhages, due to metropathia hemorrhagica, precocious and delayed puberty. For a detailed discussion of these, the reader is referred to the section on Diseases of the Ovary.

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THE SEXUAL CYCLE

DEFINITION

The more or less regular cyclic appearance and regression of fertility is referred to as the SEXUAL CYCLE. Essentially, fertility is a cyclic phenomenon in the females of all vertebrates, while the males of most species show no sexual cyclicity and are continuously fertile during the reproductive period of life. However, in hibernating animals, and in birds with a definite breeding season, the cyclic recurrence of fertile and sterile periods is also evident in the male.

It should be clearly stated at the outset that estrus (or "heat") and menstruation are two distinct manifestations of the sexual cycle; a few primates (e.g., monkeys) exhibit external signs of both estrus and menstruation.

ESTRUS is a condition during which fertile mating is possible. In this sense we may speak of estrus both in the female and in the male. Both sexual receptivity and ovulation are essential for a fertile mating and hence, in almost all animal species, these phenomena occur conjointly at estrus. Certain bats are notable exceptions; in them sexual receptivity and mating takes place in the Autumn, but the sperm remains stored in the uterus throughout the hibernating season and the ova are discharged and fertilized only during the following Spring. Mating precedes ovulation (at least by a few hours) in most mammals, but when the interval between these two essential phenomena of estrus is as long as in the bat, it becomes difficult to delimit the period of heat; here it may be better to speak of a diphasic estrus.

Under abnormal conditions one or the other characteristic manifestation of estrus (e.g., vaginal cornification, ovulation, sexual receptivity) may be induced selectively. For instance, vaginal cornification can occur without sexual receptivity in rodents treated with folliculoids, or kept on a vitamin-A deficient diet; hence no individual manifestation should be designated as estrus.

MENSTRUATION is the breakdown and shedding of a progestational endometrium; it is accompanied by bleeding from the resulting wound-surface. Menstruation occurs only in primates. It is normally due to the withdrawal of ovarian hormones from the organism of a female whose endometrium has been first developed by folliculoids and then progestationally transformed by luteoids. Even an endometrium developed only by folliculoids ("follicular-phase mucosa") will break down, with bleeding, upon the withdrawal of these hormones. Here it is incorrect to speak of menstruation and the terms "pseudomenstruation" or cyclic uterine bleeding are preferable. In primates, in which external manifestations of estrus are not prominent (e.g., higher apes, man), that period — at about the mid-interval between two menses — during which fertile mating is possible (ovulation time), corresponds to the estrus of lower animals.

COURSE

Duration. — In women the average menstrual cycle lasts 28 days, but the duration of the sexual cycle varies in the different animal species as follows:

Chimpanzee	36 days
Macacus rhesus	27 "
Pig	21 "
Cow	20 "
Sheep	16 "
Guinea pig	15 "
Rat	5 "
Mouse	4 "

In some animals (e.g., dog) there are only two estrus cycles a year, in the Spring and Autumn respectively; in others (e.g., marmot) heat occurs only once a year. Yet other animals (e.g., cat, ferret, rabbit) show almost continuous estrus with mature follicles throughout the major part of the year, but ovulation occurs only subsequent to mating; for instance after an interval of 12-16 hours in the rabbit and about 26 hours in the cat. Correspondingly we distinguish *monestrus* (one cycle per season) and *polyestrus* species.

In each estrus cycle it is customary to delimit various phases. *Estrus* coincides with the time of ovulation and sexual receptivity, *diestrus* represents the luteal phase, *proestrus* and *metestrus* are intermediate stages preceding and following the time of ovulation.

Metabolism. — The basal BODY TEMPERATURE shows very characteristic variations during the sexual cycle in women. It rises gradually during the follicular phase, just prior to ovulation there is a sudden drop and after this it remains at a high level until about 24-36 hours before the onset of the next menses. If pregnancy ensues the basal body temperature remains at the high level of the luteal phase. (See graph on p. 806.)

Regular cyclic variations in the CALCIUM, CHOLESTEROL, GLUCOSE, etc., content of the blood have also been reported, but they are too insignificant to deserve detailed discussion here.

It is noteworthy, however, that the BODY WEIGHT usually reaches a maximum at the time of menstruation, while simultaneously the blood PROTEIN and hematocrit values reach their minimum. This has been regarded as a sign of a considerable, menstrual WATER-retention, which may play a rôle in the so-called premenstrual and menstrual edema, menstrual migraine, etc.

For cyclic changes in HORMONE METABOLISM see: pp. 806, 811.

Serologic Changes. — In asthmatic women there often is an exacerbation of the symptoms just before the menses. During pregnancy a similar hypersensitivity has frequently been noted and some investigators ascribe this to ovarian hormones.

Blood. — There may be menstrual and postmenstrual LEUCOCYTOSIS, as well as an increased BLOOD-CLOTTING TIME and SEDIMENTATION RATE at the time of the flow.

Nervous System. — In women, libido and the general sense of well-being often show a peak at about the time of ovulation. In most animals the period of sexual receptivity is definitely limited to the time of estrus when ovulation makes fertile mating possible. During menstruation, women are often irritable or even slightly depressed; they tend to be restless and lose their energy, but show a great desire to clean and rearrange objects pertaining to their own person or their immediate environment. However, many of the psychic accompaniments of menstruation, including some types of dysmenorrhea, are undoubtedly due to faulty sex-education at the time of puberty (see p. 388).

Accessory-Sex-Organs. — By far the most important among the morphologic changes characteristic of the sexual cycle are those which occur in the female ACCESSORY-SEX-ORGANS, especially the *endometrium*.

The histologic changes, characteristic of the follicular and luteal phase of the cycle in various animals and man, have already been discussed on pp. 362-367 and 394. Additional information

may be gained from the adjacent series of microphotographs and graphs It is important to realize that essentially the same endometrial changes occur in menstruating and non-menstruating animals, except that in the latter the uterine mucosa is not shed, with an accompanying hemorrhage at the end of the luteal cycle, but tends to involute more gradually and without loss of blood

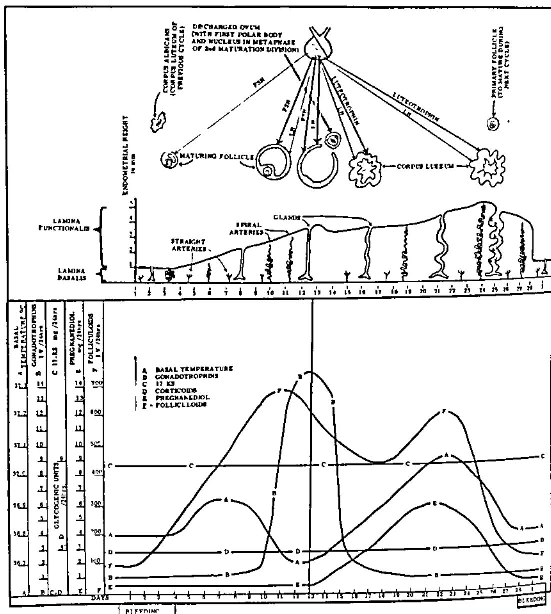


The normal endometrial cycle in man. — A. Follicular phase endometrium The glands are comparatively simple and the endometrium of medium height (low magnification). — B. Early luteal phase (secretory endometrium) The glands begin to assume a convoluted "corkscrew-like" appearance and the height of the mucosa is increased (same magnification as Fig A.). — C. Late luteal phase (premenstrual endometrium) The glands are highly developed and convoluted, the height of the endometrium has reached its maximum (same magnification as Fig A.) — D. Menstrual endometrium Only the basal layer of the mucosa remains, the rest has desquamated (same magnification as Fig A) (Cont d on p 805)



from Fig A Note high, cylindric, simple uterine stroma is fibrous — F. and F_1. High magnification ous proliferation in convoluted endometrial glands. ntervals (arrows) Note decidual transformation of from Fig. C Note extreme development of glands The stroma begins to degenerate and small hemorrhages appear in it — H. High magnification from Fig D Most of the mucosa has been shed and only the basal layer remains The surface is partly covered with blood and represents an open wound (Courtesy of Dr T Waugh)

Schematic Representation of Hormonal Interrelations During the Sexual Cycle.



In order to understand the histogenesis of menstruation it is important to realize that just prior to the onset of bleeding there is some involution of the endometrium, the decrease in height being largely due to dehydration. This regression causes further buckling of the already highly coiled spiral arteries which supply the functionalis; consequently the blood flow through the spiral arteries diminishes and there is stasis of blood with necrosis of the adjacent tissue (*Markee*, 1940). Perhaps partly under the influence of the necrotic tissue, that part of the spiral arteries which is located within the adjacent basalis, becomes constricted; this leads to a further diminution of the blood supply to the functionalis layer. Only occasionally do the stumps of the coiled arteries, in individual vascular territories, relax again and it is apparently at

this time that the loss of menstrual blood occurs. It has been suggested that "necrosin" may play a rôle in causing endometrial necrosis and vasoconstriction during menstruation, but this has not been proven.

The above-mentioned "coiled arteries," course throughout the functionalis layer and eventually end in small tufts and arterioles. There are, however, additional, shorter "straight arteries," which supply the basal third of the endometrium permitting the latter to survive even when the coiled arteries become non-functional during the menses.

Probably the initial involution and dehydration is the primary phenomenon which elicits the entire sequence of events leading to menstrual bleeding. The former is apparently a withdrawal effect mainly caused by a diminution in the folliculoid-hormone concentration of the blood, since folliculoids demonstrably augment the permeability of endometrial capillaries and correspondingly increase the transudation of water into the endometrial stroma

Regeneration of the endometrium occurs due to proliferation of the stroma and migration of epithelial cells from the mouths of the remaining gland-tubules. The vascular bed regenerates partly through outgrowths of capillaries from the stumps of the coiled arteries and partly through the transformation of straight arteries in the basalis into the coiled type.

The cervical endometrium of the human uterus also shows recognizable, cyclic variations, but these are less characteristic than those of the corpus mucosa.

The *myometrium* likewise exhibits cyclic changes in structure and function. Usually cell proliferation is most active during the follicular phase. In several animal species (e g., rabbit) contractility is also greatest at estrus, while in the luteal phase (as following progesterone injection) both spontaneous contractility, and the possibility of eliciting uterine contractions with oxytocin, are at a minimum Contrary to earlier claims this is not so in women. Here, during the follicular phase, uterine motility is characterized by low amplitude, high frequency and a tonic type of spontaneous contractions; during the luteal phase the amplitude of the contractions is often even higher, but their frequency is lower and they are not tetanic in character.

In human MENSTRUAL BLOOD there are erythrocytes (about 3,000,000/cmm.), leucocytes, vaginal-epithelium cells and fragments of endometrium. It contains small amounts of iodine (0.9 γ/gm.), arsenic (0.2 γ/gm), folliculoids (about 0.1 I.U./cc), and a toxic factor, the so-called "*menstrual toxin.*" The latter is allegedly a specific principle responsible for the toxicity of menstrual blood and perhaps, in part, even for the necrosis of the endometrium at menstruation. Some authors believe that the menstrual toxin is associated with the globulin fraction of the menstrual blood and may be identical with, or at least related to, "necrosin" (see : p. 797).

Much has been written about the *non-coagulability of the menstrual blood.* Its serum lacks fibrinogen and prothrombin, thus it resembles the serum of clotted blood. Probably menstrual blood clots before being discharged, but the clots are dissolved in utero by a fibrinolytic enzyme ("fibrinolysin"), which is actually demonstrable in it.

The *vaginal epithelium* likewise undergoes very typical cyclic variations both in animals and in women. In general it may be said that during the follicular phase the epithelium increases in height and the surface layers tend to lose their nuclei and to become cornified. These changes may be regarded as preparatory to copulation; women with hypofolliculoidism, in whom such changes do not occur, frequently suffer from dyspareunia owing to hypersensitivity of the vagina during intercourse.

For details concerning the cyclic vaginal changes in animals and women see pp. 364, 366, 395 and the adjacent photographs.


A


B


C


D



Vaginal smears during a normal 28-day ovulatory menstrual cycle. — A *2nd day of menses* — note red blood cells leukocytes mucus and many well developed epithelial cells including numerous cornified cells (Stained by Shorr Single Differential Stain J Mt Sinai Hospital p 667 1945) — B *8th day of cycle* — late postmenstrual phase, showing considerable clumping desquamation and abundant mucus Many well developed non-cornified superficial squamous cells with small pyknotic nuclei predominating — C *13th day of cycle* — ovulatory peak showing marked increase in cornified cells which are more discreet thin mucus and leukopenia — D *14th day of cycle* — postovulatory reaction leukocytosis thick mucus a decrease in number of cornified cells clumping and folding of the epithelial cells — E *18th day of cycle* — characteristic luteal reaction with marked desquamation and thick mucus clumping and folding of cells

(Courtesy of Dr E Shorr)

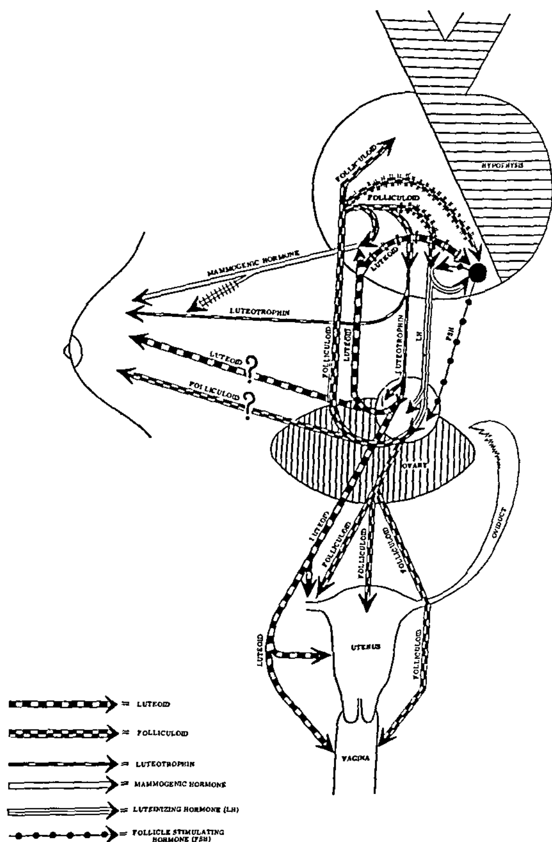
The simple or pseudostratified epithelium of the human *oviduct mucosa* is low immediately after menstruation, but increases in height during the follicular phase At this time the cells become high cylindric and are often ciliated, the nuclei assuming a marginal position. During the luteal phase the nuclei appear to be almost extruded and the cells secrete, presumably providing a nutritive shell for the ovum At the time of menstruation the secretion ceases and the cytoplasm collapses assuming the characteristic "peg-like" appearance

The *contractions of the oviduct* (readily observed by utero-salpingography) are apparently most pronounced when the ovum migrates through the tube At ovulation time the human oviduct vessels are filled with blood and the consequent erection of the fimbriæ as well as muscle contractions bring the open end into close contact with the ovary. Contractions of the oviduct, rather than the ciliary movements of its epithelial cells, are probably of the greatest importance for the migration of the ovum

The *mammary glands* tend to involute just prior to menstruation; the lumina of the tubules and lobules collapse, while the fibrous stroma shrinks and assumes a hyalinized appearance At about the 7th day of the cycle the duct and lobular epithelium proliferates, the lumina increase in diameter, the lining-cells hypertrophy, and new buds arise from the ducts Towards the end of the cycle some secretion becomes detectable within the lumina, while the stroma proliferates and assumes an edematous appearance As a result of these changes, just before menstruation, the breasts of many women become nodular to palpation, heavier, firmer and more tender than they are after cessation of the menstrual flow

Among *other cyclic variations* we might mention the development of the "sexual skin" during estrus in the monkey, marked engorgement of the nasal mucosa (especially in monkeys and women) and the characteristic "nuptial coloring" (of the plumage in birds, of the scales in certain fish). These and other pertinent changes have already been discussed in the section The Ovary

The MALE ACCESSORY-SEX-ORGANS show characteristic variations only in animals with a seasonal heat (e g , certain fish reptiles, birds).



(For legend see p 811)

HORMONE METABOLISM DURING THE SEXUAL CYCLE

The metabolism of the ovarian and pituitary hormones, which participate in the sexual cycle, has already been discussed in the sections : The Hypophysis (page 251) and the Ovary (page 372). The adjacent schematized diagrams are merely given in order to facilitate the correlation of all these data with the various phases of the cycle.

The most prominent facts which emerge from pertinent studies are :

(1) The FOLLICULOID hormone concentration of the urine rises from a very low level after the menses to a peak at about ovulation time; this is followed by a slight decline and subsequently by a second premenstrual increase. During the menses the urinary elimination of folliculoids is hardly detectable.

(2) PREGNANEDIOL excretion (an indicator of progesterone formation) is negligible during the entire follicular phase but rises gradually after ovulation to a peak at about the middle of the luteal phase, it falls to very low levels a few days prior to the onset of bleeding.

(3) GONADOTROPHINS (separate estimations of FSH and LH are not yet available) are present only in negligible amounts during the entire menstrual cycle except at ovulation time.

(4) TESTOIDS, 17-KS AND CORTICOIDS remain at about the same level throughout the cycle

All these observations are consonant with the view that folliculoids are formed in increasing amounts during the development of the ovarian follicle, then their elaboration falls until the corpus luteum begins to reach its full development. At this time progesterone formation, as judged by the urinary pregnanediol concentrations, runs parallel with folliculoid elimination. Ovulation is elicited by an increased gonadotro-

Hormonal interrelations during the sexual cycle

(Read this diagram beginning at the large, black dot in the anterior-lobe The arrows which end in a target organ without continuing into other arrows indicate purely morphogenic effects. Simple arrows mean stimulation, cross-hatched arrows, inhibition) The diagram attempts to visualize that *FSH* acts upon the ovary and causes follicle maturation This is a purely morphogenic effect which in itself does not stimulate hormone production However FSH also initiates the production of LH, which subsequently induces folliculoid hormone production by the follicle Then *LH* transforms the mature follicle into a corpus luteum and stimulates the latter to produce folliculoids but it does not cause luteoid formation If follicle maturation has not proceeded far enough for luteinization LH itself can elicit an FSH discharge to correct this The *folliculoids* cause 'estrus changes in the uterus, oviduct and vagina, they prepare these structures for the subsequent action of progesterone It is questionable whether folliculoids exert any important direct effect upon the mammary tissue, but they act back upon the pituitary, enlarge the anterior-lobe and inhibit both FSH and LH production, they stimulate luteotrophin and (especially in combination with progesterone) mammogenic hormone secretion *Luteotrophin* maintains the structure and function of already existing corpora lutea, but does not form new ones Luteotrophin also stimulates secretion in a previously developed mammary gland The *luteoids* formed under the influence of luteotrophin cause 'luteal phase' changes in the uterus, vagina and oviduct They act back on the anterior-lobe and inhibit FSH (not LH) production The growth of the breast is mainly dependent upon direct stimulation by '*mammogenic hormone*" although this effect may be augmented by simultaneous treatment with steroids (e g , folliculoids and luteoids) Apparently the proliferative stimulus exerted by mammogenic hormone' inhibits the secretory activity of the breast, in agreement with the general rule that actively proliferating cells do not secrete It is probably for this reason that milk secretion frequently fails to occur in well-developed breast tissue even in the presence of much luteotrophin *The cyclicity of the female sexual cycle* may perhaps be explained by the periodic production of FSH and LH with a resulting increased formation of folliculoids the latter in turn inhibit FSH and LH formation to a point where the ovary fails to form sufficient folliculoids to maintain this inhibition and then FSH and LH production rises again so that the process is re-initiated

phin formation, while menstrual bleeding is due to the "withdrawal phenomenon" occasioned by the involution of the corpus luteum and the subsequent fall in folliculoid and luteoid production. 17-KS, testoid and corticoid production show no cyclic variations which would indicate a participation of these hormones in the phenomena of female sexual cyclicity.

STIMULI INFLUENCING THE SEXUAL CYCLE

Since the female sexual cycle depends primarily upon the ovary it is influenced by all those stimuli which affect the latter (see . p. 374).

MECHANISM AND SIGNIFICANCE OF THE SEXUAL CYCLE

The mechanism responsible for the cyclicity of sexual phenomena has already been discussed in various sections of this book, hence only the main HORMONAL CORRELATIONS are summarized in the adjacent diagram. This hormonal mechanism is probably essentially similar in the various animal species, however, it must be admitted that most of the interpretations now generally accepted, have been derived from experiments on the rat

The most important species differences in this mechanism are due to the fact that, in animals with a *spontaneous sexual cycle* (the majority of the mammals, including man), the regulation of cyclicity appears to be mainly dependent upon interactions between the ovaries and the pituitary In *species which ovulate only upon sexual intercourse* a nervous stimulus, from the vagina and uterine cervix region, must apparently reach the pituitary to elicit the gonadotrophin discharge, which is essential for ovulation and corpus luteum formation In animals with a *seasonal estrus* (e g., bat, marmot, birds) climatic conditions (especially light) presumably play a corresponding rôle.

The SIGNIFICANCE OF THE SEXUAL CYCLE requires little comment. Sexual receptivity, the vaginal changes of "heat" and ovulation itself reach their climax at the peak of estrus and are *preparatory for mating and fertilization,* while the phenomena of the luteal phase are prerequisites of *implantation and gestation.* When fertilization fails to occur the endometrium regresses again and a new cycle is initiated, apparently in order to permit future insemination.

It is more difficult to understand the SIGNIFICANCE OF THE MENSTRUAL FLOW itself. It has been claimed that some *toxic* material must be eliminated monthly in order to maintain health, but this theory is hardly tenable since hysterectomy exerts no detectable detrimental effects upon the well-being of women.

The *lunar theory* attempted to establish some connection between the typical 28-day-cycle of women and the lunar month. These, as well as many other pertinent theories have now been abandoned.

The *embryotrophic theory* compares menstruation with the so-called proestrus bleeding, this occurs in several mammals (e g., dog, cow) just before estrus, in others (monkey) approximately at the mid-interval when menstruation occurs in man It has also been noted that erythrocytes appear in the uterine lumen at the time of implantation in a variety of animals. In women the so-called "missed period" which is the first sign of pregnancy, is quite commonly accompanied by an almost imperceptible loss of blood. According to the embryotrophic theory this slight hemorrhage at the time of implantation would be useful in furnishing nourishment to the developing embryo if fertilization had occurred. Otherwise the hemorrhage goes further and takes the form of a menstrual bleeding.

Although the latter theory is most generally accepted, no adequate data are yet available to explain the significance of the menstrual blood loss. It is quite possible that the latter has *no useful purpose* and is merely an unavoidable consequence (in some species) of the structural changes which accompany the necessary cyclic alternation between the periods of sexual receptivity (follicular phase) and those during which implantation is possible (luteal phase).

DISEASES OF THE SEXUAL CYCLE

The diseases of the sexual cycle have been discussed in connection with other ovarian derangements (see pp 409-415).

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PSEUDOPREGNANCY

DEFINITION

Pseudopregnancy (or pseudocyesis) is a condition whose manifestations are similar to those of gestation, differing from the latter mainly in the absence of embryonic elements and the usually shorter duration

It is doubtful whether pseudopregnancy exists in women although certain types of prolonged luteal cycles have been interpreted as such (see: The Ovary).

COURSE

In most animal species, the duration of the pseudopregnancy period is intermediate between that of a normal luteal phase and that of gestation.

The condition is usually elicited by a nervous stimulus such as mating, stimulation of the uterine cervix and upper vagina (electrical or mechanical) or of the nipples (suckling) In some animal species even the mere sight of the male, intense electric shocks, or treatment with convulsive drugs (e.g., metrazol) suffice to produce a pseudopregnant condition (e g., rabbit), in others (e.g., guinea pig) hysterectomy exerts the same effect.

The nervous and hormonal stimuli responsible for the development of pseudopregnancy will be discussed on p 815; they are also illustrated in the diagrams (pp. 824, 831) summarizing hormonal correlations during pregnancy, pseudopregnancy and lactation. In most animal species gestation commences as a pseudopregnancy, since

phin formation, while menstrual bleeding is due to the "withdrawal phenomenon" occasioned by the involution of the corpus luteum and the subsequent fall in folliculoid and luteoid production. 17-KS, testoid and corticoid production show no cyclic variations which would indicate a participation of these hormones in the phenomena of female sexual cyclicity.

STIMULI INFLUENCING THE SEXUAL CYCLE

Since the female sexual cycle depends primarily upon the ovary it is influenced by all those stimuli which affect the latter (see: p 374).

MECHANISM AND SIGNIFICANCE OF THE SEXUAL CYCLE

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species. Since, prior to the formation of the placenta, the ovaries are the sole important source of progesterone, the pseudopregnancy changes due to luteoids are of course also interrupted by selective removal of the corpora lutea only. Conversely, progesterone (either alone or, much more effectively, following folliculoid hormone "priming") induces pseudopregnancy-like changes even in ovariectomized or prepubertal females

High doses of folliculoids tend to transform the corpus luteum of pseudopregnancy into a large corpus luteum of "pregnancy-type" and greatly increase progesterone formation: however at the same time they so affect the endometrial lining that it can no longer respond to trauma with the usual deciduoma formation, so characteristic of pseudopregnancy.

MECHANISM AND SIGNIFICANCE OF PSEUDOPREGNANCY

It is clear from what has been said above, that normally, pseudopregnancy is elicited by nervous stimuli (especially mating or nursing), which cause a discharge of pituitary gonadotrophins especially LH and luteotrophin. The former causes ovulation and corpus luteum formation, the latter maintains the corpus luteum and stimulates it to produce large amounts of progesterone Progesterone is responsible for most of the characteristic pregnancy-like changes, for instance in the uterus, vagina and oviduct. It apparently also causes a release of mammogenic hormone from the anterior-lobe and hence development of mammary tissue. When the corpus luteum eventually ceases to function, the endometrium breaks down and milk secretion commences These are "withdrawal phenomena" but, at least in the case of milk secretion, the withdrawal of ovarian hormones is not the immediate eliciting agent, since the presence of the pituitary is also indispensable as we shall see in the chapter on Lactation

Progesterone also inhibits FSH formation and hence follicle maturation is at a standstill during pseudopregnancy

It is still not known what limits the life span of the corpus luteum during pseudopregnancy.

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PREGNANCY

DEFINITION

Pregnancy is a condition in placentalia, during which the developing embryo is harbored within the body of its mother. It begins when the ovum is fertilized and terminates at the time of delivery

In marsupials the embryo is born before it has acquired any considerable degree of independence from its mother During this time it is kept in a pouch, inseparably attached to the mammary glands, nevertheless, in accordance with the above definition, this extrauterine life in the pouch is not considered to form part of pregnancy.

Conversely, in other species (see below) implantation of the ovum occurs only many months after fertilization, here pregnancy commences long before an intimate contact is established between embryo and mother

COURSE

Duration of pregnancy. — The duration of pregnancy differs in the various species.

As shown by the following compilation there is some relationship between the body weight of animals and the length of their pregnancy, but this is not absolute

Elephant	660 days
Rhinoceros	540 "

before implantation the presence of the embryo is immaterial for the development of pregnancy changes. Consequently, in animals which can become pseudopregnant (e.g., rat, rabbit, cat) the first pregnancy changes after mating are the same whether the male was fertile or sterile.

The most prominent changes during *pseudopregnancy are an unusually* prolonged structural and functional persistence of the corpus luteum, inhibition of follicle maturation, pregnancy-like changes in the uterus, oviduct, vagina, mammary glands, pubic ligaments and indeed in all organs which show characteristic changes during gestation.

If pseudopregnancy is elicited by mating or excitation of the cervix region, a single stimulus suffices to maintain a pseudopregnant state for the period characteristic of the animal species in question (e g., about 14 days in the rat). The pseudopregnancy of lactation on the other hand depends upon continued stimulation of the nipples and ceases as soon as nursing is discontinued. In the event of prolonged, uninterrupted nursing over many weeks the pseudopregnancy period is regularly *interrupted, from time to time, by* single estrus cycles

HORMONE METABOLISM DURING PSEUDOPREGNANCY

Hormone metabolism during pseudopregnancy is essentially the same as during early gestation There is increased formation of luteoids which is evidenced by progestational changes In women, prolonged PREGNANEDIOL excretion curves are seen when the corpora lutea persist for an unusually long time

FOLLICULOID hormone production is not at a high level during pseudopregnancy and indeed in some instances (*e.g.*, during the pseudopregnancy of lactation) there is evidence of a greatly diminished folliculoid production as judged by the absence of vaginal mucification in spite of marked progesterone secretion in animals. In women, however, folliculoid excretion in the urine may be very high during pseudopregnancy.

The initial stimulus which elicits the condition of pseudopregnancy is conducive to a sudden discharge of GONADOTROPHIN from the pituitary. This has been particularly clearly proven in the rabbit in which copulation causes pseudopregnancy only if the pituitary is left intact for at least two hours after *mating; if it is removed sooner* the follicles do not transform themselves into corpora lutea, presumably due to interference with the discharge of pituitary gonadotrophins. In women the LH elimination remains approximately normal and this helps to differentiate conditions of pseudocyesis from true pregnancies.

There is indirect evidence of prolonged secretion of LUTEOTROPHIN since the corpora lutea are maintained in structure and function throughout pseudopregnancy.

Judged by the pronounced development of the mammary glands, the MAMMOGENIC HORMONE production must *also be augmented* during pseudopregnancy.

STIMULI INFLUENCING PSEUDOPREGNANCY

It has already been mentioned that HYPOPHYSECTOMY, if performed immediately after mating, prevents the development of the corpus luteum of pseudopregnancy. It *should be added* that at any time during pseudopregnancy, hypophysectomy causes the immediate cessation of progesterone production *and involution of* the already formed corpora lutea. This is due to the fact that in the absence of placental luteotrophin the corpus luteum is entirely dependent upon the pituitary for its maintenance.

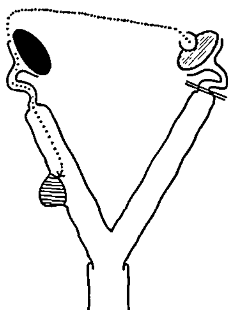
OVARIECTOMY likewise interrupts pseudopregnancy at any time in all

The contractions and ciliary motility of the oviduct apparently help the MIGRATION OF THE OVUM. If a segment of oviduct is surgically reversed, sterility ensues owing to the inability of the ova to descend past this segment. The oviduct epithelium secretes a protective shell around the ovum: this is voluminous in birds but quite inconspicuous in most mammals.

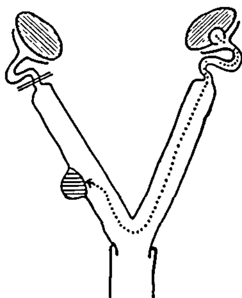
Ovarian hormones are important for the migration of egg-cells through the oviduct, since experiments in the rabbit have shown that destruction of the corpora lutea delays the downward passage of ova.

In rare instances an ovum discharged from one ovary migrates down the tube of the contralateral side after passing through the free peritoneal cavity. This is referred to as *external transmigration*. In animals with a bicornate uterus (e.g., cat) *internal transmigration* (down the uterus on the side of the ovary from which the ovum came and up the contralateral horn with implantation on the opposite side) is also possible, but only in species in which the cervix for the two uterine horns is common If two distinct cervices open separately into the vagina (e g., rabbit) such internal transmigration does not take place

Schematic Representation of Internal and External Transmigration.



External transmigration



Internal transmigration

To prove the possibility of external transmigration one ovary was removed, in experimental animals, and the tube on the opposite side was transected between two ligatures. After this intervention pregnancies did not occur on the side on which the oviduct was occluded, but on the side from which the ovary was removed. This could only be due to external (transperitoneal) transmigration. Conversely, mere ligature of one oviduct proved compatible with implantation of embryos on that same side. This could only be the result of internal transmigration as shown by the above drawings.

Horse	337	"
Cow	284	"
Man	280	"
Rhesus monkey	168	"
Pig	115	"
Guinea pig	70	"
Cat	63	"
Dog	60	"
Ferret	41	"
Rabbit	30	"
Mouse	20	"
Rat	21	"
Hamster	16	"
Opossum	14	"

The stimuli capable of influencing the duration of pregnancy will be discussed below (see. p 820).

Fertilization. — In most animal species the OVUM IS DISCHARGED from the follicle soon after the FIRST POLAR BODY HAS FORMED, when the spindle of the second maturation division is in the metaphase. A few cells of the cumulus oöphorus remain attached to the ovum *and apparently furnish it with nourish*ment. Perhaps the hyaluronidase of the spermatic fluid helps to dissolve these granulosa cells, thus clearing the way for the penetration of the sperm and subsequent fertilization.

The ASCENT OF THE SPERM into the tube is so rapid that it could not be accounted for by the slow locomotive *power with which its flagellum can move* it forward (about 3 mm./min.). In the *dog and guinea pig mobile spermia* were found in the tube 20 minutes, and in the rat 2 minutes, after copulation. Probably uterine contractions and, to a lesser extent, ciliary movements of the oviduct-epithelium are mainly responsible for this rapid ascent.

The spermium is not indispensable for fertilization; it is important mainly as a carrier of the paternal genetic characteristics. It has been claimed that *mere exposure to cold can induce cleav*age even in mammalian ova and thus produce parthenogenesis, *e.g., in the* rabbit (*Pincus and Shapiro*, 1940). A few cell divisions are often seen in mammalian ova retained in ovarian follicles, this is a beginning of parthenogenesis which may explain some of the ovarian teratoid tumors. (See: Ovarian Teratoids.) In lower vertebrates *partheno*genesis is quite common.

In most mammals FERTILIZATION IS POSSIBLE ONLY DURING A FEW DAYS AT OVULATION TIME. In the rabbit, in which many pertinent investigations have been performed, the ovum remains viable but a few hours after its discharge from the follicle and even sperm, which is somewhat *more* resistant, retains the power to fertilize only about *48 hours after its introduction into the* female accessory-sex-organs. In a few species (e g., bats), however, the spermia remain viable for longer periods after mating. (See: p. 802.)

Progesterone can prevent fertilization of artificially ovulated eggs. In the rabbit this effect is demonstrable if the hormone is administered before insemination. *It is immaterial if it is given* by injection or endogenously produced by corpora lutea formed *after* treatment with gonadotrophin.

In women, conception is also most likely to occur at ovulation, that is, during the mid-menstrual period, while just prior to, during and after the menses sexual intercourse rarely leads *to pregnancy*. It is therefore customary to refer to the pre- and post-menstrual days as the "*safe period*," an expression which is perhaps not *entirely* beyond criticism, since it *takes for* granted that intercourse is decided upon for motives other than reproduction. This relationship between fertility and the phase of the menstrual cycle was mainly clarified by the Japanese physician *Ogino*, and the Austrian investigator *Knaus*, and hence it is sometimes designated as the Ogino-Knaus or "O.K" rule. The writer disapproves of the use of an abbreviation in this instance.

Implantation. — Immediately after fertilization, the OVUM EJECTS ITS SECOND POLAR BODY and begins its descent through the tube into the uterus; it is during this passage that cleavage of the ovum commences.



Experimental production of deciduomas and metrial glands in the rat. — A. Cross-section through the uterus of a spayed female rat in which a deciduoma was produced by scratching the endometrium (3 days earlier) after pretreatment with folliculoids and progesterone Note marked proliferation of the decidual cells which almost completely occlude the uterine lumen. — B. Cross-section through the uterus of a rat in which a deciduoma was produced under similar conditions, but the picture was taken on the 11th day after traumatization At this time most of the deciduoma tissue became necrotic and was cast off into the lumen, since the life span of these neoplasms is limited Note marked development of 'metrial gland' in the mesometrial wall of the uterus Similar metrial glands are normally observed under the placental insertion in pregnant rats — C High magnification of the typical deciduoma cells from the deciduoma shown in Fig A Note polymorphonuclear decidua-like cells with prominent nucleoli — D. Comparatively light glycogen containing cells, such as are normally seen in the basal part of experimental deciduomas (near the mesometrial insertion). One cell (arrows) contains an eccentric nucleus and numerous deep eosinophilic granules (black on photograph) Similar cells invade the entire mesometrial wall and are characteristic of the 'metrial gland' region — E Medium magnification of the central blood-pool in an experimental deciduoma Note large blood vessels (arrows) which empty directly into this pool (cross) which corresponds to the intervillous space of the placenta Its development in the absence of an embryo indicates that it is not due to active erosion by the latter

In most animal species (e.g., rat, mouse, guinea pig, monkey, rabbit, man) IMPLANTATION USUALLY OCCURS BETWEEN THE 6th AND 9th DAY after mating.

Only in a few animals (e.g., armadillo, deer) IS DELAYED IMPLANTATION the rule. In the deer for instance, fertilization takes place in August and cleavage begins immediately, but it goes only to the stage of blastocyst formation, then development ceases until December when implantation occurs. Thus, in this species, the total length of gestation is nine months, but actually almost the entire development of the embryo is completed during the last five months.

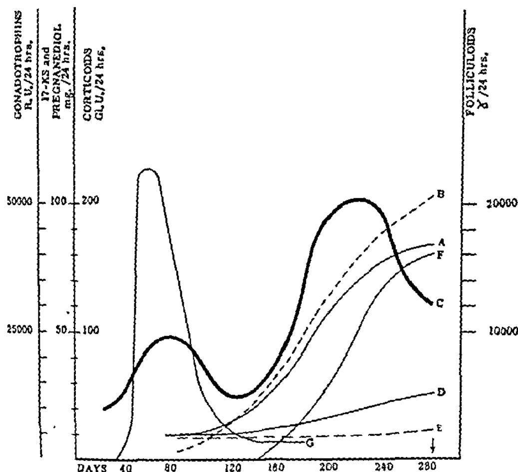
Under certain experimental conditions implantation may be artificially delayed. This is the case for instance in the mouse and rat if fertilization occurs immediately after delivery (at the postpartum estrus) and pregnancy ensues during lactation. While normally in the mouse implantation takes place on the 7th day after mating, in lactating mice free blastocysts are found in the genital passages as late as the 16th day and hence the length of pregnancy is prolonged. It has been thought that luteoids play an important rôle in this *delay of implantation or that some factor* necessary for implantation is lost through the milk, but the cause of this strange phenomenon has not yet been definitely determined

In some animal species, IMPLANTATION OCCURS IN TWO STAGES. Thus, for instance, in the rat and rabbit the ovum first nidates in the endometrium on the antimesometrial side, but after some time chorionic villi facing the lumen of the uterus invade the endometrium on the opposite (mesometrial) side and form the placenta there. At the time of this second implantation (in the rat the 10th day after mating) some blood oozes into the uterine cavity and a few days later erythrocytes can be detected in the vaginal smears. This is the so-called "PLACENTAL SIGN," which serves as an early indication of pregnancy. In women, at the time of the first "missed-period," a similar slight bleeding may also occur and is often misinterpreted as a true menstruation.

The STRUCTURE OF THE PLACENTA differs essentially in the various species. If the chorionic epithelium is merely attached to the epithelium of the endometrium we speak of "*epithelio-chorial,*" if it erodes the epithelium and attaches itself to the connective tissue of "*conjunctivo-chorial,*" if it penetrates to the endothelium of the maternal blood vessels of "*endothelio-chorial*" and finally if it actually enters the maternal blood-vessel lumina of "*hemo-chorial*" placentæ. Man as well as many other mammals (e.g., apes, monkeys, rodents) have a hemo-chorial placenta, that is to say, that affording the greatest possible degree of contact between fetus and mother.



polynuclear giant cell syncytia.



Excretion rates of the various hormones in pregnancy (average values of the cases studied). — A pregnanediol — B folliculoids — C corticoids — D 17-KS (DNB method) — E 17-KS ($SbCl_3$ method) — F theoretical excretion curve for the pregnanolones assuming that the increase in difference between the two KS curves is due to them — G Gonadotrophins (After E.-H. Venning, Endocrinology 39, 203, 1946.)

pend upon the ovary throughout gestation, the life of the placenta itself is independent during the later stages. In the rat, for instance, ovariectomy causes abortion whenever it is performed, but *if the embryos are removed together with the ovary* the placenta remains intact. Examination of the uterine contents in ovariectomized pregnant rats revealed that here the resulting acute involution of the uterine muscle so compresses the gestation-sac that the placenta is detached and the embryo dies. However, if the embryo is removed and the amniotic fluid is discharged at the time of spaying, the resulting compression is less severe and the placenta lives to the end of its normal life-span (e.g., in the rat the 21st day after mating). Significantly the placenta of such animals, at least partially maintains the mammary glands, uterus and vagina. This must obviously be ascribed to placental hormones since these organs were maintained, as long as the placenta remained intact, even in rats deprived both of their anterior-lobe and of their ovaries.

In ovariectomized rabbits abortion can be prevented by very large doses of PROGESTERONE alone, but smaller doses suffice if the luteoid is given in combination with appropriate doses of folliculoids. A proportion of follicu-

In several animals (e.g., rat, mouse) large, granular epithelial cells develop in the myometrium just below the placental insertion. These are referred to as the "*metrial gland.*" They are alleged to furnish nutritive material to the embryo by holocrine secretion of disintegrating cells discharged into the afferent placental vessels. Their exact significance has not yet been established.

Metabolic and Organ Changes. — The metabolic, structural and functional changes characteristic of pregnancy are essentially the same as those previously discussed in connection with pseudopregnancy, although they are generally much more pronounced, especially in the second half of gestation. Only the great increase in metabolism due to the growth of the fetus, especially the considerable increase in caloric, protein and mineral requirements, deserve special mention here.

HORMONE METABOLISM DURING PREGNANCY

The characteristic changes in hormone metabolism, which occur during pregnancy, have already been discussed in the section on the ovary and are summarized in the adjacent diagram. The EXCRETION of pregnanediol, folliculoids and pregnanolones increases gradually and rather rapidly during the last two-thirds of gestation, while that of the 17-KS shows only a very slight rise The urinary elimination of gonadotrophins reaches a maximum towards the end of the second month and falls to comparatively low levels when the excretion rates for the first mentioned four products begins to rise sharply. The corticoid elimination in the urine shows a double-peaked curve, with one maximum coincident with the peak of the gonadotrophin excretion and a second maximum between the 200th and 240th day of gestation.

Intermedin elimination rises so regularly and markedly during pregnancy that urinary bioassays (on hypophysectomized frogs) can be used as a safe indication of gestation instead of the *A-Z* or other gonadotrophin tests.

It will be noted that all these data are gathered from observations on women and, as stated elsewhere, in other mammals the changes in hormone metabolism during gestation do not follow the same pattern.

Comparatively little work has been done concerning the HORMONE CONTENT OF VARIOUS TISSUES in pregnant women, because only the amniotic fluid and the placenta are readily available for such examinations. The placenta is an extraordinarily rich source of gonadotrophins (especially LH) as well as of various folliculoid hormones (see: p 84) and indirect evidence (see below) indicates that the placenta also produces mammogenic hormone, luteotrophin, luteoids and perhaps even testoids The amniotic fluid is especially rich in folliculoids.

STIMULI INFLUENCING PREGNANCY

In all animal species so far examined, OVARIECTOMY prevents implantation, if performed while the ova are still free and causes abortion if performed at any time *during the first weeks of gestation*. Selective removal of the corpora lutea has the same effect and it is justified to assume that ovariectomy acts mainly, if not entirely, through the resulting corpus luteum hormone deficiency *During the second half of gestation* the corpus luteum is necessary for the maintainance of pregnancy in certain species only (e.g., rat, mouse, rabbit), while in others (e.g., cat, guinea pig, dog, man) ovariectomy later in pregnancy is compatible with delivery at the normal time In women, ovariectomy after the second month does not necessarily cause abortion.

Presumably in the course of gestation the placenta takes over the functions of the ovary. This process goes so far in certain species that the ovarian contribution to progesterone production becomes dispensable.

Probably, even in species which de-

In the rabbit, TESTOSTERONE *(in comparatively large doses of 10-20 mg./day) prevents implantation if given early and causes fetal death if administered later during pregnancy.* This action of testosterone is especially noteworthy since the compound is known to be luteoid as judged by the progestational transformation test. *Other testoids* (e.g., methyl-testosterone or ethynyl-testosterone), far from causing abortion in intact rabbits, actually prevent the interruption of pregnancy which would normally ensue following ovariectomy in this species; thus these compounds exert typical luteoid actions even as judged by this test.

DESOXYCORTICOSTERONE acetate (which is also luteoid) likewise prevents abortion in the ovariectomized rabbit

REMOVAL OF OTHER ENDOCRINE GLANDS AND INJECTION OF VARIOUS OTHER HORMONES can cause abortion, but this is probably due to the nonspecific damaging effect of the treatment and does not imply any important participation in the regulation of gestation by endocrine glands other than the hypophysis, ovary and placenta.

Among the DIETARY MEASURES which can influence pregnancy, *vitamin E deficiency* is especially noteworthy, since it selectively damages the placenta and thus causes abortion. Vitamin E deficiency does not have any adverse effect upon the pituitary, the ovary, fertilization or even implantation, it results in abortion merely due to the inability of placental tissue to develop normally in the absence of this food constituent

MECHANISM AND SIGNIFICANCE OF THE PREGNANCY CHANGES

The nervous and hormonal stimuli responsible for the development of pregnancy changes have already been discussed above and are summarized in the diagram on p 824.

Suffice it to re-emphasize here that in most animals PREGNANCY COMMENCES AS A PSEUDOPREGNANCY, hence the first changes characteristic of this condition are independent of the developing ovum. In some animals (as well as in man) the normal luteal phase of the cycle corresponds to this first, "pseudopregnant" period of gestation.

After implantation the embryo begins to intervene through the developing placenta. At first, however, only the ovary produces the hormones necessary for the maintenance of pregnancy (luteoids) and only under the influence of anterior-lobe gonadotrophins. Later the placenta gradually takes over the function of the pituitary and through its own gonadotrophic hormones causes the pregnancy-corpora-lutea to be maintained in a functional condition; thus the placenta, by way of the ovary, assures its own maintenance. In a still later stage of development (at least in certain species) the placenta becomes entirely independent of both ovary and pituitary inasmuch as it produces sufficient quantities of luteoids to maintain itself. Perhaps luteoid production by the placenta is under the influence of placental gonadotrophins, but this has not been proven and it is also possible that the placenta elaborates luteoids without any gonadotrophic hormone stimulation.

PROGESTERONE is probably the most important hormone necessary for the maintenance of gestation It is essential for (1) the life of free ova before implantation, since the latter degenerate following castration if no progesterone is given, (2) the progestational proliferation of the endometrium in preparation of implantation, since the typical "endometrial lace" does not develop in the absence of this hormone; (3) the formation of the deciduoma-like maternal placenta following the trauma of the nidating ovum; (4) the subsequent growth of the "metrial gland" underneath the placental insertion; (5) the development of the "intervillous space" and (6) the particular myometrial growth, characteristic of gestation

loids/luteoids of 1/750 to 1/1600 appears to be optimal. If proportionately more folliculoid is given abortion ensues, due to the positive abortive effect of such compounds, while if the dose of progesterone is proportionally raised the "antiabortive" properties of the luteoid compound are not fully utilized due to inadequate sensitization by the folliculoids. As stated in the section on the steroids the optimal *synergistic proportions of folliculoids and luteoids* vary according to the species, the target organ under consideration, and the absolute dose level at which the mixture is given. The important fact to retain, however, is that progesterone requires the synergistic effect of folliculoids in order to be fully effective in the maintenance of pregnancy, but large doses of folliculoids counteract this gestation-maintaining effect of corpus luteum hormone

Large doses of FOLLICULOIDS prevent implantation in all animal species so far examined, but they cause interruption of an already established gestation only in the rabbit. In the cat, abortion can be produced by folliculoids during the early stages of gestation, but this becomes increasingly more difficult as pregnancy progresses. In women neither folliculoids alone, nor even a combination of folliculoids and oxytocin, cause abortion; although such combined treatment may facilitate delivery of a dead fetus.

HYPOPHYSECTOMY *during the first half of gestation* is incompatible with implantation and the maintenance of pregnancy, presumably because at this time the anterior-lobe is the only source of the luteotrophin necessary to maintain functional corpora lutea

Hypophysectomy performed *during the second half of gestation* is compatible with the maintenance of pregnancy in some species (e.g., rat, cat, guinea pig, mouse,) while in others (e g , rabbit) fetal death and abortion ensue after hypophysectomy, whenever the operation is performed. Apparently the placenta gradually also takes over the gonadotrophic — especially the luteotrophic — hormone production of the pituitary. This is clearly shown in experiments on the rat, in which after hypophysectomy during the second part of gestation even the corpora lutea are maintained as long as the placenta remains intact.

The *rôle of the posterior-lobe* is somewhat less clear. Hypophysectomy, or selective removal of the posterior-lobe alone, does not significantly impede delivery and has no effect on the normal "aging" of the placenta. Nevertheless at delivery difficulties due to weak uterine contractions are comparatively common in hypophysectomized animals, thus suggesting that oxytocin discharge from the posterior-lobe is important at this time It is also noteworthy that the pituicytes of the posterior-lobe hypertrophy and proliferate at delivery (e.g., rat) and that lesion of the supraoptico-hypophyseal tract during pregnancy causes atrophy of the posterior-lobe (with diabetes insipidus), accompanied by definite derangements in uterine contractility at delivery (e g , cat).

Oxytocin given alone does not cause abortion in the mouse, but in combination with folliculoids it interrupts pregnancy, although folliculoids in themselves have no such effect.

Immediately following the REMOVAL OF THE PLACENTA the corpora lutea involute in *all* species so *far* examined, presumably because their maintenance depends upon placental luteotrophin.

The placenta is surprisingly independent of the embryo nourished by it. REMOVAL OF THE EMBRYO does not significantly alter the development and life-span of the placenta In rhesus monkeys, in which the embryo was removed on the 70th day of gestation, delivery occurred at approximately the normal time on the 157th day.

It is especially important to emphasize that, contrary to the assumptions of earlier investigators, the chorion need not erode maternal tissue in order to form the intervillous space, since the latter develops even in experimental deciduomas, that is, in the absence of a fertilized ovum, if the uterus of a progesterone pretreated animal is traumatized

The rôle of the unusually large amounts of FOLLICULOIDS, produced during pregnancy especially in man, is not clearly understood; probably they sensitize the organism to the actions of luteoids and, together with the latter, stimulate the mammogenic hormone production of the hypophysis, thus preparing the breast for lactation. The general mitosis-stimulating effect of folliculoids may also play a rôle in the development of the embryo, but this has not yet been definitely established.

The purpose of the excessive GONADOTROPHIN production during the first half of gestation is likewise not clear. Perhaps the gonadotrophins help to stimulate the ovary (and placenta?) to produce the necessary large amounts of ovarian hormones.

DISEASES OF PREGNANCY

Only the most important diseases of pregnancy can be discussed here, for further details see the textbooks of gynecology and obstetrics.

Ectopic Pregnancy. — The problem of ectopic pregnancy has already been touched upon in the section on endometriosis. (See p. 467.)

Implantation does not occur in the uterus unless the endometrium is especially prepared and transformed into a progestational mucosa, yet ectopic implantation in the oviduct or the free peritoneal cavity can occur and under such conditions a fetus may fully mature and be delivered, by cesarean section, in viable condition.

Animal experiments have shown that embryos removed from the uterus can be successfully transplanted into ectopic locations (e g , the uterus of another animal or the peritoneal cavity of the mother) and may continue to grow there. Spontaneous ectopic pregnancy could be explained in two ways. Either implantation occurs on progestationally transformed endometrial tissue islets (e g , in the peritoneum) or tissues other than the endometrium can, under spe-

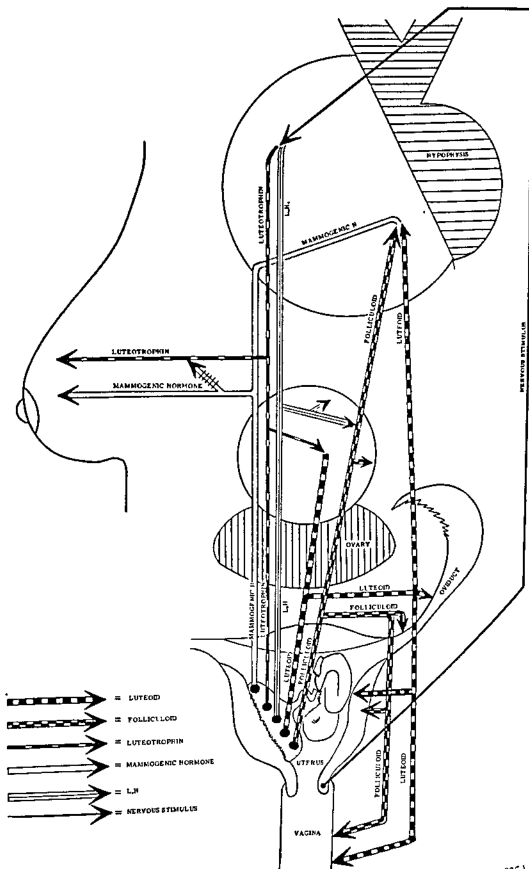
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Hormonal correlations during pregnancy and pseudopregnancy

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LH and luteotrophin production *LH* transforms the mature follicle into a corpus luteum, it also stimulates folliculoid hormone production, but the latter is inconspicuous during pseudopregnancy. Increased and prolonged secretion of *luteotrophin* causes persistence of the corpus luteum and *progesterone* formation Progesterone induces progestational changes in uterus, oviduct and vagina. It also stimulates *mammogenic hormone"* production by the anterior-lobe and this in turn produces acinar development in the breast In spite of considerable luteotrophin production, milk secretion does not occur during pseudopregnancy, presumably because this effect cannot become manifest in the presence of the strong breast-proliferation caused by the "mammogenic hormone"

When the *placenta* becomes hormonally functional it secretes "mammogenic hormone", luteotrophin, LH, luteoids and folliculoids, but in most species including man it produces little, if any, FSH The effect of these hormones is similar to the corresponding principles secreted by the anterior-lobe and ovary respectively Hence, during the later stages of gestation, the placenta may substitute for the function of both ovary and anterior-lobe. Here they are indicated as forming a common hormone-pool in the blood Apparently due to a synergism between the direct gonadotrophic effects of luteotrophin and folliculoids upon the ovary, the corpora lutea become greatly enlarged during gestation.



(See legend on p 825)

teins is the causative derangement. A *variety of endocrine disturbances* (e.g., thyroid or parathyroid deficiency, adrenal cortex hyper- or hypofunction) have also been considered to be of etiologic significance, but it must be admitted that the pathogenetic mechanism of this condition is still obscure.

A rise in gonadotrophin and a fall in folliculoid and pregnanediol excretion often accompany late pregnancy toxicoses but the significance of this derangement is not known The low pregnanediol values may result from progesterone deficiency or from pregnanediol retention due to failure of its conjugation with glucuronic acid.

THERAPY with folliculoids or progesterone (singly and in combination) have been recommended by various investigators, but the results are not striking

Among non-endocrine therapeutic measures, venesection, decapsulation of the kidney, lumbar puncture, treatment with magnesium sulphate, chloralhydrate and other sedatives, as well as protection against light (to which these patients are very sensitive), are important. In very severe cases, however interruption of gestation is the only effective treatment

Other Diseases. — Among other diseases of pregnancy DYSTOCIA (prolonged, difficult and painful labor), due to an oversized fetus, resistance of the soft parts, or uterine inertia, OSTEOMALACIA, due to the excessive calcium requirements of the developing fetal skeleton and DERMATOSES OF PREGNANCY are noteworthy

It has been suggested (on purely theoretic grounds) that the EMOTIONAL CRISES, as well as the often profound somnolence of pregnant women, could be due to the production of anesthetic steroids, especially since pregnanedione, an oxidation product of pregnanediol, proved highly effective in causing first, excitation and later somnolence and anesthesia in experimental animals

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LACTATION

DEFINITION

Lactation is the period during which the mother nurses her offspring Milk or colostrum secretion may begin in certain species (e g, man) before delivery and may continue some time after weaning, it can also occur in babies of both sexes during the first few days after birth or under the influence of disease at any time. In these cases we may speak of galactorrhea, colostrum, or even milk secretion, but it is better not to refer to these conditions as lac-

cial conditions, serve as a medium for the implantation of fertilized ova.

Successful transplantation of embryos with their placentæ *from the uterus into the peritoneum is compatible with* either theory since, unwittingly, endo*metrial cell-islets could be transplanted* together with the placenta. Neoplastic placental tissue can certainly grow in almost any tissue as judged by the metastases of chorionepitheliomas.

Habitual abortion. — It is generally assumed that habitual abortion may be due to progesterone deficiency, hypothyroidism or vitamin-E deficiency and should be treated in these cases with progesterone, thyroid extracts and *vitamin-E respectively. In theory, thyroid therapy appears to be least well-founded, especially when applied to women without manifest signs of hypothyroidism, yet among the measures mentioned above it is most frequently claimed to have been successful. Progesterone therapy is to be recommended especially if the pregnanediol excretion is subnormal.

Hydatidiform mole and Chorionepithelioma. — As we have repeatedly stated in this book, certain tumors of the placenta, the hydatidiform mole and *the chorionepithelioma, retain the ability of normal placental tissue to produce* excessive amounts of gonadotrophins. *Up to one million I U /liter have been* found in such cases. It is noteworthy that hydatidiform moles may allegedly lead to the production of large quantities of FSH which is normally almost entirely absent from the urine of pregnant women. Even the spinal fluid and especially the tumor tissue itself are rich in gonadotrophins in such cases The urinary folliculoid and pregnanediol values, however, are generally not unduly high.

Hyperemesis gravidarum. — The nausea and vomiting of pregnancy, is usually most manifest in the morning It is said to be accompanied by a slight rise of *the urinary gonadotrophins* above the normal level, while the folliculoid and pregnanediol excretion re*mains normal.*

The etiology of this condition is still unknown, but progesterone treatment is claimed to be of benefit in some cases. Psychotherapy and prescription of low-residue, carbohydrate-rich diets are advisable.

Pre-Eclampsia and Eclampsia. — The term PRE-ECLAMPSIA designates a derangement of pregnancy characterized by albuminuria, hypertension, oliguria, edema, *precordial* pain, headache, visual disturbances and various nervous manifestations. We speak of ECLAMPSIA *when these same symptoms* are very pronounced and convulsions with multiple hemorrhages appear, especially *in the liver and kidney. There are* also thrombotic processes in various vascular territories, necrosis of the liver, decreased CO_2-combining power, markedly lowered pH and increased blood uric acid. The disease is often fatal and usually occurs during the last three or four months of gestation.

Eclampsia has been ascribed to *basophilic invasion of the posterior pituitary* and was claimed to be related to atherosclerosis of old age (*Cushing*) Later, excessive production of *posterior-lobe hormones,* with subsequent multi*ple hemorrhages* due to vasoconstriction and inhibition of diuresis (*Anselmino et al.*) was thought to play an im*portant rôle in the* pathogenesis of eclampsia. However, this interpretation was mainly based on the alleged, but not *definitely proven,* presence of much vasopressor and antidiuretic hormone in the blood and urine of eclamptic women.

It may be taken for granted that the *placenta* plays an outstanding rôle, since eclampsia invariably *vanishes after* delivery or abortion.

It has been claimed that some *allergic hypersensitivity* to placental pro-

these interventions do not cause abortion) results in a considerable atrophy, but not in a complete involution of the mammary glands, because placental hormones partly maintain the breast.

OVARIAN HORMONES tend to inhibit milk secretion if administered during lactation. Folliculoids are very active in this respect while luteoids are practically inert. An especially pronounced inhibition of milk secretion is obtained when folliculoids and luteoids are simultaneously administered during lactation. In the complete absence of luteoids (e.g., after ovariectomy) only this combination treatment is effective, while folliculoids alone fail to inhibit lactation. Large amounts of TESTOSTERONE (but not methyl-testosterone) likewise inhibit milk secretion (e g , rat).

In animals and man PREGNANCY during lactation tends to decrease the milk yield but does not abolish it.

Selective REMOVAL OF THE EMBRYO during pregnancy has no effect upon the mammary glands or upon the initiation of lactation following subsequent delivery of the placenta at the end of pregnancy.

The REMOVAL OF THE PLACENTA together with the embryo initiates lactation almost at any time during pregnancy, if the mammary glands are already adequately developed It is interesting in this connection that as long as placental remnants remain in the uterus after delivery, milk secretion is also inhibited in women This is presumably due to the secretion of ovarian hormones by the placental remnant.

NEURO-HUMORAL CORRELATIONS DURING LACTATION

In considering the physiology of lactation it is customary to distinguish between three stages (1) development of the mammary glands; (2) initiation of lactation; (3) maintenance of milk secretion

Gonadotrophin treatment in immature animals (e.g , rat) causes pronounced luteinization of the ovaries and DEVELOPMENT OF THE MAMMARY GLANDS, but no secretion If, however, in such animals the ovaries are subsequently removed, when the mammary gland is already fully developed, secretion sets in soon after spaying. This is probably due to pituitary-luteotrophin since no lactation ensues if the hypophysis is removed simultaneously with the ovaries. Apparently a fall in the ovarian hormone concentration of the blood is necessary to permit this effect of hypophyseal luteotrophin The following theory may explain this observation · presumably the ovarian hormones stimulate the formation not only of luteotrophin, but also of much hypophyseal mammogenic hormone, which causes mammary-gland proliferation. Most glands do not secrete while they are very actively growing, hence this growth-stimulating effect in itself could inhibit the secretagogue effect of the luteotrophin; the latter is obviously produced in these gonadotrophin treated animals since they possess functional corpora lutea. After spaying, removal of the ovarian hormones so diminishes mammogenic hormone production that now the luteotrophin can stimulate milk secretion.

The factors responsible for the INITIATION OF LACTATION are essentially independent of the act of *nursing*, since the mammary glands begin to secrete before suckling commences

As previously stated, hypophysectomy during the second half of gestation fails to prevent the onset of milk secretion, although it interrupts lactation if performed at any time after delivery. This suggests that the hypophysis is likewise not essential during this first stage. Presumably the placenta can produce all the necessary hormones required for the full development of the breast (folliculoids, luteoids and

tation. — *True lactation* is accompanied by characteristic changes in the ovaries, uterus, etc., which are not necessarily present under other conditions conducive to mammary secretion.

COURSE

At the end of pregnancy, often a short time before delivery, the breast *begins to secrete* a fluid particularly rich in degenerating leucocytes (colostrum bodies) which is referred to as "COLOSTRUM." Only somewhat later does the secretion assume the characteristic features of true milk.

During lactation there is ANESTRUS or AMENORRHEA in most animal species. At the same time the maturation of follicles is inhibited so that ovulation and corpus luteum formation cannot occur. As a result of these ovarian changes at least the first stages of lactation are accompanied by sterility.

In some animals (e.g., mouse, rat) 24 to 36 hours after delivery there is a POSTPARTUM ESTRUS with ovulation and corpus luteum formation. At this time fertilization may occur so that these animals may become pregnant during lactation. The corpus luteum resulting from this postpartum estrus is referred to as the CORPUS LUTEUM OF LACTATION. In other species (e.g., cat) there is no postpartum ovulation and the corpora lutea of lactation are formed by reactivation of the corpora lutea of pregnancy. The corpus luteum of lactation persists longer than that of the ordinary cycle, yet in the event of very prolonged lactation (e.g., if several successive litters are nursed by the same rat) occasional estrus cycles, with ovulation and corpus luteum formation, occur periodically.

The UTERUS undergoes rapid involution during lactation. The nervous stimulus of nursing appears to play a prominent rôle since this atrophy is delayed after delivery if the offspring are removed.

Unlike during the diestrus of pregnancy, the VAGINAL epithelium of the rat is not mucified during lactation. Presumably, in the doses in which it is normally produced, progesterone alone is not sufficient to cause vaginal mucification, sensitization with folliculoids being essential; accordingly, folliculoids administered to a lactating rat cause vaginal mucification.

HORMONE METABOLISM DURING LACTATION

Little is known about the hormone metabolism during lactation beyond the fact that the luteotrophin content of the anterior-lobe tends to rise. Some investigators claim to have found luteotrophin in the urine at this time, presumably because the pituitary produces an excessive amount of it in order to maintain milk secretion. The increased LUTEOID and decreased FOLLICULOID hormone production, characteristic of the lactation period, have already been mentioned elsewhere.

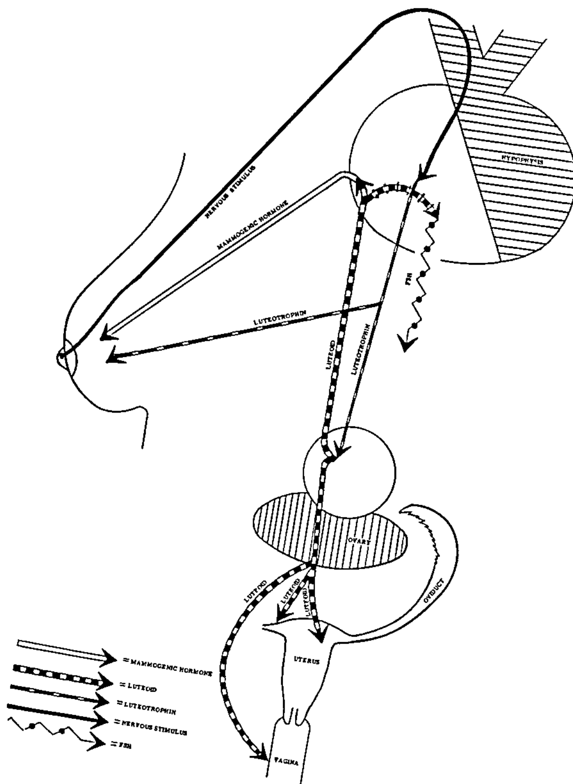
STIMULI INFLUENCING LACTATION

HYPOPHYSECTOMY during lactation almost immediately inhibits the secretion of milk in all animal species so far examined. Curiously however, if the pituitary is removed during the second half of gestation in species in which this intervention does not cause abortion (e.g., rat), no significant change in the mammary glands is observed until delivery: at this time milk secretion begins in a normal manner. Apparently the initiation of lactation, unlike its maintenance, is independent of the hypophysis.

OVARIECTOMY, far from inhibiting it, usually increases milk secretion during the lactation period. This is presumably due to the removal of the milk-secretion-inhibiting ovarian hormones.

SIMULTANEOUS OVARIECTOMY AND HYPOPHYSECTOMY during the second half of gestation (in species in which

LACTATION



(See legend on p 830)

mammogenic hormones) and the onset of milk secretion (luteotrophin).

Since *abortion* elicits temporary milk secretion at any time during the latter part of gestation, it is reasonable to assume that the onset of milk production is a "withdrawal phenomenon," somewhat comparable to *menstruation*.

The MAINTENANCE OF LACTATION depends upon a neuro-humoral reflex, the so-called "suckling reflex." This consists of an afferent, nervous and an efferent, humoral part. The nervous stimulus of suckling causes a continuous discharge of luteotrophin from the anterior-lobe and thus maintains lactation, as long as the nursing is continued; after weaning, lactation ceases because luteotrophin production is no longer maintained. Formerly it was believed that the emptying of the milk-ducts is the secretory stimulus necessary for the maintenance of lactation and that in the absence of nursing, the accumulation of milk in the breast causes pressure atrophy of the glandular parenchyme. Experiments in the rat have shown, however, that as long as a litter is nursing the breast, milk secretion continues even if the removal of the secretory products is prevented by ligature of the milk-ducts. Indeed under these conditions the pressure in the mammary glands may become so great that the parenchyme ruptures and a milky edema may infiltrate the entire breast region. It is probable that the afferent nervous pathway of this neuro-humoral reflex traverses the spinal cord, since it is abolished by cord-transection.

The maintenance of the corpus luteum of lactation, the accompanying diestrus (or amenorrhea) and the lactational involution of the uterus, are also conditioned by the suckling reflex, since prevention of milk secretion by ligature of the milk-ducts does not influence these changes as long as the nursing stimulus is applied.

The suckling reflex may even initiate all the phenomena characteristic of lactation without a preceding gestation. Thus, experiments on non-pregnant rats have shown that if they are attempting to nurse the litter of another female, they fail to ovulate and their corpora lutea persist for an unusually long time. Simultaneously, vaginal estrus ceases, the endometrium becomes progestational and the mammary glands begin to proliferate; indeed eventually sufficient milk-secretion occurs to enable such rats (or mice) to act as foster-mothers for the litters of other animals, providing them with all the milk required for their development.

When it became known that prolactin and luteotrophin are the same substance, the problem arose why the luteotrophin necessary for the maintenance of the highly functional pregnancy corpora lutea fails to cause milk secretion during gestation. Perhaps, as explained above, the simultaneously produced large quantities of mammogenic hormone cause such marked proliferation of the breast that it fails to respond to luteotrophin, although large quantities of the latter are present in the body even before delivery. (For further details see the adjacent diagram illustrating neuro-humoral correlations during lactation.)

Hormonal correlations during lactation

During lactation little "mammogenic hormone" is produced, since, then its secretion is stimulated only by luteoids and not by folliculoids. In this small quantity it causes but slight mammary growth which apparently does not interfere with the activity of luteotrophin. Since the ovarian luteoids inhibit FSH production, follicle maturation is at a standstill and progestational transformation of the sex organs is slight.

ANTIHORMONES AND OTHER TYPES OF ACQUIRED RESISTANCE TO HORMONES

Historic Introduction. — *Möbius* (1906) was probably the first to express the idea that hormones can be neutralized by certain substances which circulate in the blood. He found that the blood of thyroidectomized sheep neutralizes the action of thyroid hormone. Preparations of such blood have been made available commercially under the name of "ANTITHYREOIDIN MÖBIUS." Some clinicians claim to have obtained beneficial results with this preparation in Graves' disease, but the results were by no means striking and hence this treatment fell into disuse

Subsequently *Blum* (1933) obtained an antithyroid preparation from normal blood which he called "KATECHIN." This is apparently identical with the substance marketed under the name "TYRONORMAN," which has also been claimed (without much proof) to be highly effective in the treatment of thyrotoxicosis. *Schäfer* (1924) termed such inhibitory hormones "CHALONES

Abderhalden (1918) observed that the blood of experimental animals chronically treated with extracts of endocrine glands, contains specific defensive ferments, the 'ABWEHRFERMENTE". these have the property of selectively destroying the hormones of the corresponding endocrine cells The so-called "CYTOLYSINES" should also be mentioned in this connection They are specific immune substances, formed against the protein of certain foreign cells, which have been introduced into the body. After such treatment these cytolysines appear in the blood and if the latter is injected into other (recipient) animals, they cause more or less specific destruction of those organs with whose extracts the donor animal had been pretreated

None of these antisubstances are identical with the ANTIHORMONES as subsequently defined by *Collip* et al (1934).

The Antihormones. — The first observations really pertinent to the antihormone problem were those showing that the thyroids of guinea pigs chronically treated with thyrotrophin (*Aron*, 1930), or the ovaries of mice receiving prolonged gonadotrophin administration (*Zondek*, 1931), eventually cease to react to the trophic hormones with the usual hypertrophy and hyperplasia Indeed, AFTER VERY CHRONIC TREATMENT WITH TROPHIC HORMONES THE END-ORGANS (THYROIDS, OVARIES) BECOME AS ATROPHIC AS AFTER HYPOPHYSECTOMY

That this phenomenon is actually one of specific immunity to trophic hormones. and NOT SIMPLY DUE TO AN EXHAUSTION OF THE END ORGANS, has also been proven. Rats rendered insensitive to pregnancy-urine gonadotrophin, by continuous pretreatment, still reacted with intense ovarian enlargement when treated with a pig pituitary gonadotrophic extract. Furthermore, gonadotrophin injected intravenously into rats is normally demonstrable in the blood for many hours, but it disappears almost immediately if injected into animals rendered resistant to the same gonadotrophic preparation by chronic pretreatment.

The CLASSIC EXPERIMENTAL ARRANGEMENT which led to the discovery of the antihormones and is still in use in pertinent studies is the following :

A group of animals (the *donors*) is injected with a hormone preparation until they become resistant to its specific effects Then blood is taken from these donors and injected into a second group (the *recipient or test animals*) simultaneously with a normally active dose of the hormone preparation with

DISEASES OF LACTATION

During the first days postpartum, PAINFUL ENGORGEMENT of the breast ("caked breast") may develop, especially if the baby is not allowed to nurse. In such instances folliculoids and (less reliably) testoids may bring relief. *Folliculoids do not completely inhibit milk* secretion in women although they do so in the rat. This could be due to the *fact that both luteoids and folliculoids* are necessary for this milk-suppressing effect and in women, unlike in the rat, a corpus luteum of lactation does not always develop. In keeping with this interpretation, rats spayed during lactation (and thus deprived of their corpora lutea) show no significant inhibition of milk secretion if treated with folliculoids. Perhaps here again the milk-suppressing effect is due to the production of excess mammogenic substance under the influence of the ovarian hormones.

GALACTORRHEA is a condition in which milk secretion continues in the absence of nursing. In women it is often accompanied by ovarian atrophy, uterine atrophy and amenorrhea, similar *to that of normal lactation. Hyperinvolution* of the uterus and prolonged amenorrhea may also occur in mothers who nurse their babies for an unusually long time, but in most women the menses reappear before the baby is weaned.

In galactorrhea, as in patients in whom lactation must be suppressed for other reasons, combined treatment with folliculoids and luteoids is recommended.

If MILK PRODUCTION IS INSUFFICIENT treatment with luteotrophin would appear to be the rational therapy, but up to now the results are not very encouraging.

In some instances, especially in animals (e.g., goat, cow) treatment with small doses of folliculoids increases milk production. The mechanism of this action has not been fully explained, but perhaps it is due to increased luteotrophin production, without any excess stimulation of mammogenic hormone secretion.

Occasionally, women fail to resume their menstrual cycles after childbirth even if they do not nurse their babies for an unduly long period. In some instances (especially after complicated deliveries) this may be due to the so-called POSTPARTUM TYPE OF SIMMONDS' DISEASE (see : Simmonds' disease), but in others it is unaccompanied by any sign of anterior-lobe deficiency and then the underlying pathogenic mechanism is difficult to explain.

OTHER DISEASES OF THE BREAST (*e.g., cystic hyperplasia*, excessive or precocious development) are discussed in the section : The Ovary.

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with a certain gland extract may fail to antagonize the effects of extracts made from the same material by a different chemical procedure.

(3) *Organ specificity*, that is, antihormones produced by pretreatment with an extract of a certain organ may fail to antagonize preparations of the same hormone made (with the same method) from another organ of the same species (e.g., differences in antigonadotrophic hormones developed by injection of pituitary, placental and urinary LH.)

(4) *Hormone specificity*, that is, antihormone obtained by treatment with one hormone is ineffective against the action of another hormonal principle (e.g., *antithyrotrophin against gonadotrophin*).

Space does not permit a detailed discussion of all relevant problems; suffice it to say that all antihormones are strictly hormone specific, but their species, extract and organ-specificity, though often pronounced, is not absolute.

The cruder the extracts and the greater the possibility of protein denaturation in the procedure used for their purification, the more likely are they to produce antihormones. This is in agreement with the immune-body theory.

Up to now most of the experimental work has been done in connection with the ANTIGONADOTROPHIC AND ANTITHYROTROPHIC HORMONES, but there is a good deal of evidence suggesting the possibility of producing ANTILUTEOTROPHIN, ANTISOMATOTROPHIN as well as *ANTIHORMONES AGAINST SOME OF* THE METABOLISM-INFLUENCING ANTERIOR-LOBE PRINCIPLES. The claim that certain impure CORTICOID extracts may also lead to antihormone formation requires further confirmation especially since this would be the only instance of an antihormone against a *non-protein* hormone.

Other types of acquired resistance to hormones. — It is not known *whether the insulin insensitivity*, which sometimes develops in diabetics chronically treated with INSULIN (very exceptional), is due to antihormone formation or to some other metabolic adjustment.

Chronic treatment with PARATHYROID extract leads to resistance against the usual effects of the hormone, but this is not due to antihormone formation and indeed is not a true insensitivity but rather a reversal of the hormone's actions (see : Parathyroids).

The mechanism of "*tachyphylaxis*" to RENIN and VASOPRESSIN is not yet *fully understood but there is no proof* of antihormone formation to these substances.

The inability to maintain a progestational endometrium indefinitely by PROGESTERONE injections, appears to be due to an acquired insensitivity of the target organ (in this case the endometrium).

The inability to maintain thymus atrophy by chronic DESOXYCORTICOSTERONE *treatment is an example of* "dissociated adaptation", here the blood contains no specific antihormone and the resistance does not extend to all other actions of this steroid.

The inability to inhibit somatic growth with initially effective but low doses of FOLLICULOIDS is likewise unaccompanied by the appearance of antihormones in the blood. This is not even a hormone-specific adaptation since ani*mals rendered resistant to the growth*-inhibiting action of a natural folliculoid, are also resistant to the same effect of an artificial folliculoid whose chemical structure is entirely different. Here we appear to be dealing with an effect which is specific to a certain hormone *action but not to a particular hormonal* compound.

which the donors had been pretreated. A third group of animals (the *controls*) receive only the active dose of the hormone preparation, without blood from the resistant donors. If the blood of the pretreated donors contains specific antihormones, the recipients, treated with blood and hormone do not react while the controls, treated with hormone alone, show the usual effects of the endocrine preparation employed.

Using essentially this same type of experimental technic it has been demonstrated that ANTIHORMONES ARE FORMED BY VARIOUS MAMMALS, INCLUDING MAN, against gonadotrophic and *thyrotrophic* preparations made from the glands of diverse animal species.

Antihormone formation naturally limits the therapeutic efficacy of the trophic hormones when they have to be administered for long periods.

The SOURCE of the antihormones is still unknown, but it has definitely been established that the responsive target organ (e.g., the ovary in the case of gonadotrophin, the thyroid in that of thyrotrophin) is not essential for their formation, since antigonadotrophin is normally formed by spayed and antithyrotrophin by thyroidectomized animals. The hypophysis is likewise not essential, since hypophysectomized animals are also capable of forming antihormones. On the other hand, "blockade" of the reticulo-endothelial system especially if combined with splenectomy, appears to diminish or abolish the ability to form antihormones, just as it impedes the formation of true serologic antibodies.

Up to the present time true antihormone formation has been definitely demonstrated only in animals pretreated with protein hormones. Adaptation and resistance may be acquired to other types of hormones (e.g., vasopressin, progesterone) but this is not due to antihormone formation.

Although the blood of normal animals contains certain hormone-antagonizing substances it is doubtful whether these are identical with the antihormones obtained by *hormone-pretreatment*. NATURAL HORMONES, PRODUCED BY ENDOCRINE GLANDS, DO NOT APPEAR TO EVOKE THE FORMATION OF ANTIHORMONES. This explains why hyperfunctional pituitary tumors can maintain a condition of hyperpituitarism for an almost unlimited period and that in parabiosis experiments, in which a spayed animal is united with an intact partner, the hyperfunctional pituitary of the former indefinitely continues to stimulate the ovaries of the latter.

The CHEMICAL NATURE of the antihormones is not yet known, but like the serologic immune bodies they appear to be in the pseudoglobulin and euglobulin fractions of the serum and can be purified by iso-electric precipitation.

All these observations suggest a close relationship between antihormones and true serologic immune bodies. However, the typical in vitro reactions (complement fixation, precipitation, flocculation, agglutination), as well as the anaphylactic and skin reactions characteristic of immune bodies, are not regularly obtained with antihormones, hence the theory has been advanced that the *antihormones represent a new type of blood substance closely related to, but not identical with the typical immune bodies*.

In connection with the SPECIFICITY OF THE ANTIHORMONE ACTIONS it is customary to distinguish:

(1) *Species specificity*, that is, antihormones produced by pretreatment with gland-extracts of one species may fail to antagonize the effects of similar extracts made from the glands of another species.

(2) *Extract specificity*, that is, antihormones produced by pretreatment

THE GENERAL-ADAPTATION-SYNDROME AND THE DISEASES OF ADAPTATION

DEFINITIONS AND TERMINOLOGY

Experimental and clinical observations have shown that in addition to the specific adaptive reactions (e.g., serologic reactions to specific antigens, muscular hypertrophy subsequent to physical work, proliferation of the epidermis where the skin is exposed to pressure or friction) there are certain physiologic mechanisms which help to raise resistance to damage as such. The endocrine system plays a prominent part in these latter reactions which occur irrespective of the specific nature of the evocative damaging agent.

The sum of all those non-specific, systemic reactions of the body which ensue upon long-continued exposure to stress has been termed the "GENERAL-ADAPTATION-SYNDROME." It is characterized by a number of morphologic and functional changes. Among the most prominent of these are enlargement of the adrenal cortex with increased corticoid-hormone secretion, involution of the thymus and of other lymphatic organs, gastrointestinal ulcers, certain metabolic changes and variations in the resistance of the organism.

If an individual is continuously exposed to stress, the resulting general-adaptation-syndrome evolves in three distinct stages:

(1) The ALARM REACTION, which is defined as the sum of all non-specific systemic phenomena elicited by sudden exposure to stimuli to which the organism is quantitatively or qualitatively not adapted — Some of these phenomena are only passive and represent signs of damage or "shock" (e.g., hypothermia, hypotension, hemoconcentration, increased capillary permeability, hypochloremia, depression of the nervous system), others are manifestations of active defense against shock (e.g., adrenal-cortical enlargement, increased corticotrophin and corticoid production, hyperchloremia). If the eliciting stress is of medium intensity, the alarm reaction tends to evolve in two distinct phases, the phenomena of shock being followed by those of counter-shock. However, in most cases the manifestations of shock and defense are intermixed; indeed the sequence of events may even be reversed, e.g., in the case of progressively increasing fatal stress. Here some counter-shock develops first, when the body can still resist, but subsequently, shock-manifestations become increasingly more prominent as the augmenting intensity of the stress makes further resistance impossible.

(2) The STAGE OF RESISTANCE is defined as the sum of all non-specific systemic reactions elicited by prolonged exposure to stimuli to which the organism has acquired adaptation. It is essentially a "protracted counter-shock". Resistance is increased to the particular agent to which the body had been exposed, and this is usually accompanied by a marked decrease in resistance to other types of stress. The impression is gained that during the stage of resistance adaptation to one agent is acquired "at the expense of" resistance to other agents.

(3) THE STAGE OF EXHAUSTION represents the sum of all non-specific systemic reactions which ultimately develop as the result of very prolonged exposure to stimuli to which adaptation had been developed, but could no longer be maintained.

The three stages of the general-adaptation-syndrome are illustrated in the graph (cf p. 838), based upon measurable variations in resistance to

This chapter is based upon the monograph "STRESS", by H. Selye, Acta Endocrinologica Inc., Publ. Montreal Canada 1949 (For brief review of this book see p. 867.)

Prohormones. — It has been found that before antigonadotrophic properties appear in the serum of an animal treated with a gonadotrophin, there may be a phase during which the serum augments, rather than inhibits, the action of the gonadotrophic extract in test animals. It has been suggested that this effect is due to the formation of a "PROGONADOTROPHIC HORMONE," a substance which may be an antihormone against an antigonadotrophic principle in the extract used for pretreatment. This progonadotrophic substance is also found in the globulin fraction of serum and is active in hypophysectomized as well as in normal test animals of both sexes. Its nature is not yet clear

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cepts and terms which are more or directly related to it.

HOMEOSTASIS (*Cannon*) is the tendency of living organisms to maintain a steady internal equilibrium, that is, to preserve an unchanging "milieu intérieur" as the great French physiologist Claude Bernard termed it. It is due to specific homeostatic mechanisms that the blood sugar tends to remain constant in spite of continuous glucose combustion or exogenous glucose administration. The maintenance of the body temperature despite changes in the temperature of the surrounding medium and the maintenance of a constant blood volume after hemorrhage or intravenous fluid infusion, are other examples of such phenomena. Distinct physiologic mechanisms are responsible for the various homeostatic reactions and many of these play a part in the general-adaptation-syndrome, which, in the final analysis, is due to the combined effect of coördinated adaptive reactions.

SHOCK has never been clearly defined, but it is a state of profound mental and physical depression elicited by a variety of non-specific damaging agents (trauma, acute infections and intoxications, burns, X-rays, nervous stimuli, etc.). It is mainly characterized by nervous depression, hypothermia, hypochloremia, tissue catabolism and other signs of damage. It has been regarded as a passive manifestation of damage unrelated to the phenomena of defense. In the light of the general-adaptation-syndrome concept, shock is merely the first phase of this syndrome which — unless it is of fatal severity — automatically elicits the chain of reactions necessary for the increase in resistance to stress.

TACHYPHYLAXIS OR SKEPTOPHYLAXIS ("quick readiness" and "lightning-readiness" respectively) are terms suggested for certain phenomena of non-specific resistance. Among these we might mention the resistance which develops immediately following intravenous injection of toxic tissue extracts, vasopressin or renin. In their original formulation, the terms designate a state in which resistance is increased not only to the preparations with which the animals were pretreated, but also to other toxic tissue extracts. This apparently corresponds to the counter-shock-phase of the alarm reaction.

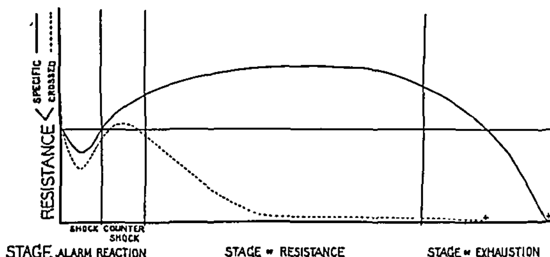
The term "BIOPHYLAXIS" has been introduced to designate non-specific defense mechanisms (e.g., phagocytosis, inflammation) exclusive of true immune reactions, while the word "TROPHOPHYLAXIS" describes the increased resistance of mice to cobra venom, following the administration of a "nutrient" such as glucose, milk, etc. Both these ill-defined terms are mentioned merely in order to avoid confusion with other phonetically similar names.

The "CRISE CARYOCLASIQUE" of *Dustin* is a sudden increase in the number of pyknoses, especially in the thymus and lymph glands, of animals treated with the so-called "poisons caryoclasiques." It was thought that these represent a specific class of drugs, but it is now generally recognized that the "crise caryoclasique" is merely one manifestation of the alarm reaction and is due to the involution of lymphatic tissue, caused by excess corticoids. This was clearly proven by the observation that adrenalectomy prevents the "crise caryoclasique" unless corticoids are administered.

The "CRISE HÉMOCLASIQUE" of *Widal* was defined as a syndrome of leukopenia, decrease in the refractive index of the serum, decrease in blood-clotting time and blood pressure, sometimes accompanied by albuminuria and fever. It is elicited by acute infectious diseases, cold and other types of non-specific damage. Probably this syndrome also consists of manifestations of the alarm reaction.

The "SYNDROME POLYPEPTIDO-TOXIQUE" of the French literature, which develops in acute hepatic insufficiency or after burns and trauma, is characterized by an unusually high polypeptide concentration in the blood; it evidently also belongs to this group. The extensive protein breakdown characteristic of the alarm reaction is probably the cause of the increase in blood polypeptides.

The concept of "NON-SPECIFIC THERAPY" is based on the claim that administration of certain non-specific damaging substances leads to the production of "metabolites" which increase resistance to various diseases ("Leistungssteigerung und Protoplasmaaktivierung"). It is probable that these phenomena are closely related to the in-



Schematic representation of the changes in specific (full line) and crossed (dotted line) resistance during the three stages of the general-adaptation-syndrome. The progress of time is indicated along the abscissa and the degree of resistance along the ordinate. Note that specific resistance to the agent with which the animal is treated decreases during the shock phase of the alarm reaction and increases during the counter-shock phase, reaching its maximum during the stage of resistance, in the stage of exhaustion, it falls below normal and finally, death ensues Crossed resistance, to agents other than that with which pretreatment occurred, falls even lower than the specific resistance during the shock phase, rises but slightly during the counter-shock phase and is definitely subnormal in the stage of resistance This indicates that while resistance to one agent (specific) is acquired by pretreatment with this same agent, resistance to other stimuli (crossed resistance) falls below the normal level (horizontal line) (After H Selye J Clin Endocrinol 6, 117, 1946)

damage: it will be kept in mind, however, that many other manifestations of the syndrome develop concurrently in the same three-stage-pattern.

Interest in the general-adaptation-syndrome has recently received a further impetus as a result of investigations suggesting that some of the most important diseases of clinical medicine (e.g., hypertension, nephrosclerosis, "rheumatic diseases") may represent by-products of the endocrine reactions which are at play in the general-adaptation-syndrome. These maladies are therefore believed to be "DISEASES OF ADAPTATION," that is, the results of excessive or abnormal adaptive reactions to stress (see: "Clinical Implications," p. 858).

By SPECIFIC RESISTANCE, we mean that type of inurement which increases resistance only against the particular type of stress to which the body had been exposed; conversely, NON-SPECIFIC RESISTANCE designates the ability of the body to withstand a type of stress qualitatively different from that to which it had become adapted.

The term "ADAPTATION ENERGY" is used to describe the ability of the organism to acquire resistance to stress.

By definition, any agent capable of producing an alarm reaction is an "ALARMING STIMULUS." Agents causing merely local damage, which requires no general adaptive adjustment (e.g., amputation of limbs) are relatively mild alarming stimuli, while those which evoke intensive adaptive responses (e.g., cold, solar or roentgen radiation, muscular exercise, nervous stress, fasting, infections, intoxications) produce severe alarm-reaction symptoms

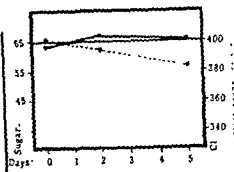
The alarm reaction is not necessarily a pathologic phenomenon since *it can* be elicited by mild exposure to stress, which is unavoidable in the course of every-day life

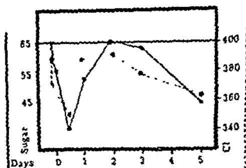
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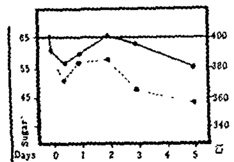
Having thus outlined the general-adaptation-syndrome, it may be well to survey its relationships to certain earlier

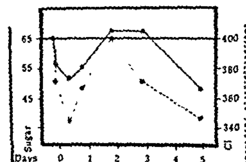
resistant stage is considerably shorter due to their inability to maintain acquired resistance.

During the resistant stage of adaptation to one type of stress — when the blood sugar has returned to or above normal — *exposure to another type of stress* tends to cause a particularly

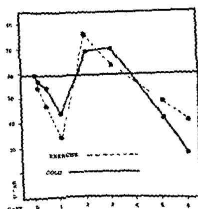








general- …cemia of …nounced … but the …ypoglyc- … to normal and the third (stage of exhaustion) by a second period of hypoglycemia, this third stage ends in the death of the animal. (After H Selye J Clin Endocrinol 6 117 1946)



Blood sugar changes in hypophysectomized rats during the general-adaptation-syndrome produced by exercise or cold. Note that hypophysectomy likewise decreases adaptability so that the general-adaptation-syndrome is 'telescoped' into a brief six-day period under the conditions of this experiment, yet the three stages are again clearly distinguishable, hypoglycemia, during the alarm reaction, return slightly above normal during the stage of resistance and secondary hypoglycemia during the stage of exhaustion. The greatly shortened stage of resistance in the adrenalectomized and hypophysectomized animal clearly show that adrenal and hypophyseal hormones are not indispensable for adaptation but they prolong the period during which resistance, to uniform and continuous exposure, is possible.

(After H Selye J Clin Endocrinol 6 117 1946)

crease in resistance seen during the above-mentioned "phylactic" reactions and during the counter-shock-phase of the alarm reaction

The theory of SEROUS INFLAMMATION (SEROSE ENTZUNDUNG) (*Rossle, Eppinger*) is based on the observation that under the influence of various noxious agents the, normally low, protein concentration of the intercellular fluid rises due to leakage of plasma into the intercellular spaces. This was referred to as "albuminuria into the tissues" and is the result of increased capillary permeability. It is accompanied by an increase in the Na,Cl and water content, and a decrease in the K and PO_4 content of the tissues. Gastrointestinal ulcers (such as occur in the alarm reaction) may accompany this syndrome in man, an observation which emphasizes the similarity between these two conditions.

The "MALADIE POST-OPÉRATOIRE" (*Leriche*) has attracted much attention, especially among surgeons, since it often occurs after extensive surgical interventions. It corresponds to the shock phase of the alarm reaction, being characterized by tissue catabolism

In *conclusion*, it may be said that numerous individual manifestations of the alarm reaction in particular, and of the general-adaptation-syndrome as a whole, have been described by various investigators under divers names It is essential to emphasize however, that all these changes are only individual manifestations of a coordinated syndrome whose ultimate aim is defense. This syndrome evolves in three distinct stages (the alarm reaction, the stage of resistance and the stage of exhaustion) and its primary biologic purpose is to raise resistance to non-specific stress In this respect, it is essentially different from the specific defense reactions (e.g., serologic reactions) which often produce a much greater degree of resistance, but only to a certain, specific type of damage.

COURSE OF THE GENERAL-ADAPTATION-SYNDROME

Metabolism. — The BODY TEMPERATURE decreases during the shock-phase of the alarm reaction, especially if defense is impeded by adrenalectomy or hypophysectomy. During the stage of resistance, on the other hand, there often is hyperthermia.

The B.M.R. is usually below normal during the shock-phase, but returns to normal during the stage of resistance.

Carbohydrate Metabolism. — The BLOOD SUGAR rises immediately following exposure to stress (emergency hyperglycemia); this is mainly due to the discharge of adrenaline. Later however, the blood sugar falls (often considerably below normal) and in fasting animals pronounced hypoglycemia may ensue. During counter-shock, the blood sugar rises again, presumably due to gluco-corticoids; it may reach hyperglycemic levels in the stage of resistance. A secondary, terminal hypoglycemia follows during the stage of exhaustion. This response is essentially the same regardless of the type of alarming stimulus used, but when the damaging agent has a specific effect upon blood sugar, this action is superimposed on that of the general-adaptation-syndrome. Thus, if the reaction is elicited by muscular exercise, the hyperglycemic peaks are relatively low and the hypoglycemia especially pronounced, because much glucose is utilized for muscular work.

In *adrenalectomized* or *hypophysectomized* animals, hyperglycemia is rarely seen during any stage of the general-adaptation-syndrome, but the three-stage-pattern of the glycemic response is maintained. There is an initial hypoglycemia (alarm reaction), a return of the blood sugar to normal (stage of resistance) and a final hypoglycemia (stage of exhaustion). The main difference between normal animals and those deprived of their pituitary-adrenal mechanism is that in the latter the

severe hypoglycemia This is another indication that adaptation to one agent tends to decrease resistance to other types of stress.

The LIVER-GLYCOGEN content diminishes simultaneously with the initial hyperglycemia during the alarm reaction, presumably because the blood sugar is formed mainly at the expense of hepatic glycogen. Contrary to most other damaging agents, exposure to low atmospheric pressure *increases the glycogen content of the liver, even in fasting animals.* Lack of oxygen depresses *sugar utilization and* — as does any other alarming agent — stimulates the endogenous production of corticoids. It is not unreasonable to assume therefore, that under the influence of glucocorticoids, a large amount of protein is transformed into sugar, but the latter — not being adequately utilized — is deposited as glycogen in the liver In agreement with this interpretation, adrenalectomy prevents hepatic glycogen *deposition* at low *atmospheric pressures*

Perhaps the exceptionally high blood sugar values *seen in thyroidectomized* animals during the general-adaptation-syndrome, could be explained on a similar basis In the absence of thyroid hormone, sugar utilization is also impeded although gluconeogenesis from protein can be increased during stress as a result of excess gluco-corticoid formation

The LACTIC ACID CONTENT of the blood increases during *the alarm* reaction, but *tends to return towards normal* in the stage of *resistance*

Lipid Metabolism. — The fat content of adipose tissue diminishes during the alarm reaction returns to or above normal in the stage of resistance, but declines again in the stage of exhaustion During the alarm reaction, lipid *deposition in the liver* is often noted, *perhaps due to a transfer from adipose* tissue caused by corticoids.

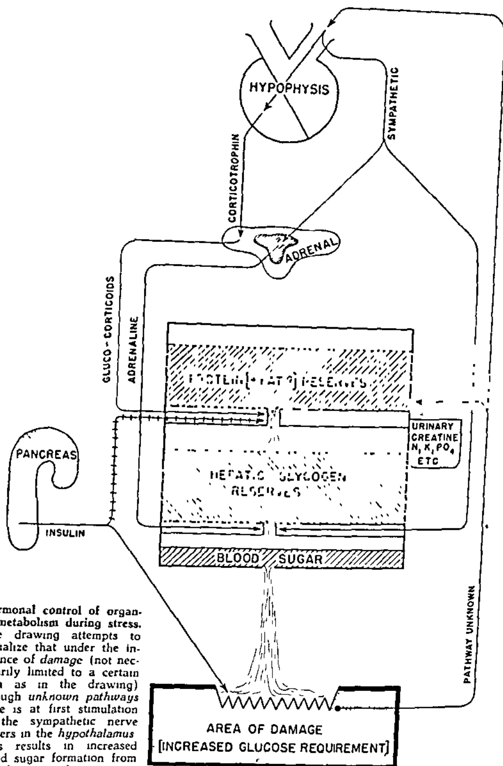
The CHOLESTEROL *content of the* adrenal cortex is low during the alarm reaction and the stage of exhaustion, but normal or high in the stage of resistance. Serum cholesterol values show less striking variations.

Nitrogen Metabolism. — The pronounced break-down of body protein during the alarm reaction and the stage of exhaustion are accompanied by *an* increase *in the total* N.P N , *as well as* the POLYPEPTIDE, AMINO-ACID, UREA and URIC ACID *content of the blood.* At *the same time the nitrogen* balance becomes markedly negative. None of these changes are manifest during the stage of resistance.

The urinary elimination of CREATINE is greatly augmented in the alarm reaction and the stage of exhaustion, but not during the stage of resistance.

The BLOOD GLOBULIN and FIBRINOGEN increases at the expense of the ALBUMINS after burns, traumatic shock and other types of stress. *It is* rather *probable that an important fraction of those protein-catabolites*, which *appear in the* blood *during the alarm reaction, originate* in the lymphatic organs as a result of the lymphocyte-destroying property of corticoids This is especially likely for the uric acid derivatives, which are plentiful in lymphatic organs, since corticotrophin and corticoids cause a marked rise in the uric acid content of blood and urine. It must be remembered, however, that PROTEIN-CATABOLISM during stress cannot be mediated solely by corticoids since it is not prevented by *adrenalectomy* Probably *the break-down of most body-proteins* (except those of *the lymphocytes)* are independent of the adrenal cortex, although the utilization of protein-catabolites for gluconeogenesis or protein re-synthesis (e g., for regeneration) is greatly aided by the corticoids

Mineral Metabolism. — A pronounced decrease in blood CHLORIDES is one *of the most* constant changes in *the shock-phase, and often also* occurs *during the stage of exhaustion* In the resistant phase, the *chloremia is normal*



Hormonal control of organic metabolism during stress. The drawing attempts to visualize that under the influence of *damage* (not necessarily limited to a certain area as in the drawing) through *unknown pathways* there is at first stimulation of the sympathetic nerve centers in the *hypothalamus*. This results in increased blood sugar formation from the hepatic glycogen reserves. The latter is due partly to the direct effect of *sympathin* — liberated at the hepatic nerve endings — and partly to *adrenaline* discharged as a result of splanchnic irritation — This mechanism immediately yields a large amount of free sugar, but is of limited duration. In more chronic emergencies — again through unknown pathways — the anterior-hypophysis is stimulated to produce an excess of *corticotrophin* which in turn augments adrenal *gluco-corticoid* secretion. The gluco-corticoids promote glycogen formation from protein (and fat?) and the "protein transposition" essential for regeneration. *Insulin* inhibits (cross-hatched arrow) gluconeogenesis from non-sugar reserves and thus antagonizes the gluco-corticoids, yet it also promotes glucose utilization in the area of damage to promote regenerative phenomena and resistance.

adaptation occurs, as the "stage of exhaustion."

The non-specific or "crossed-resistance" (that is, resistance to an agent other than that to which inurement is acquired) is likewise characteristically influenced by the general-adaptation-syndrome. During the shock-phase, the non-specific resistance decreases even more than the specific resistance. In the counter-shock-phase on the other hand, there is an increase in the ability of the organism to withstand various types of stress, not only that to which it had been previously exposed.

This crossed-resistance is never as great as the specific resistance to the agent with which the alarm reaction had been produced. It has been assumed — though by no means proven — that the crossed-resistance during the counter-shock-phase is, at least partly, due to increased endogenous corticoid production.

Growth and Bones. — Somatic growth is inhibited during exposure to stress, especially in the alarm reaction and exhaustion stages of the general-adaptation-syndrome. This has been ascribed to a "shift in pituitary-hormone formation," due to the fact that in emergencies an increased production of the life-maintaining corticotrophic hormones is accomplished at the expense of other, less urgently needed, hypophyseal principles such as somatotrophin, the gonadotrophins, luteotrophin, etc. (Cf. diagram on p. 857.)

Perhaps deficiency in growth hormone and excess of corticotrophin (causing catabolism of the organic bone-matrix) are also largely responsible for the osteoporosis caused by systemic stress.

Specific bone lesions do not normally occur during the general-adaptation-syndrome, although certain types of arthritis are probably accompaniments of maladaptation (cf. p. 863). In this connection, it is noteworthy that certain pituitary extracts and desoxycorticosterone frequently produce arthritis in the rat, while corticotrophin and corticoids proved beneficial in rheumatoid arthritis.

Blood.— The BLOOD-CLOTTING TIME decreases during the alarm reaction, while fibrin formation is accelerated. This is in accord with the clinical observation that, following surgical operations the platelet-count rises while the clotting time falls. At the same time there is usually a rise in blood fibrinogen, an acceleration of blood-corpuscle sedimentation and a tendency towards "blood-sludging". The frequent occurrence of thrombosis after operations and burns may be related to these changes. They are at least partly due to adrenaline liberation, since this hormone markedly increases blood fibrinogen and accelerates clotting.

The "BLEEDING TIME" is likewise shortened by exposure to alarming stimuli.

The BLOOD-PRESSURE rises immediately after exposure to stress, probably because of the emergency secretion of adrenaline. Later, the hypotension characteristic of shock supervenes, but during the stage of resistance there is a tendency to develop hypertension and nephrosclerosis, especially under certain experimental conditions, to be discussed below.

The BLOOD-COUNT shows very characteristic changes during the alarm reaction. There is a pronounced increase in the total white-cell-count, due to neutrophilic leukocytosis with eosinopenia and relative or even absolute, lymphopenia. These changes are particularly obvious in the counter-shock-phase and may be preceded by leukopenia during the shock-phase especially if the damage is severe. Animals in which the leukopenia persists for an unduly long period are usually irresistant and succumb without showing any signs of counter-shock. The lymphopenia of the alarm reaction is presumably elicited through the same pituitary-adrenal mechanism which is responsible for the involution of the lymphatic tissue. Adrenalectomy tends to inhibit the lymphopenia and eosinopenia of stress. Adrenaline raises the lymphocyte count;

or even increased. The hypochloremia of the alarm reaction is not due to increased chloride loss through the urine, since it cannot be prevented by bilateral nephrectomy and the urinary chloride excretion is actually diminished during the shock-phase. Probably the hypochloremia is due to an increased leakage of chlorides into the intercellular spaces and — in the event of transudate formation — into the large body cavities (pleura, peritoneum, joints).

The blood SODIUM concentration tends to run parallel with that of the blood chlorides, although its variations are much less marked.

The blood POTASSIUM content rises during the shock-phase, probably due to a discharge of intracellular potassium which accompanies the catabolic phenomena characteristic of this reaction. We do not yet have conclusive data concerning the potassemia during the later phases of the general-adaptation-syndrome.

The hypochloremia, hyponatremia and hyperkalemia of the shock-phase are reminiscent of the electrolyte changes caused by adrenal insufficiency. This is in agreement with the conception that a state of "relative cortical insufficiency" exists during the first phase of the alarm reaction.

The PHOSPHATE content of the blood is increased during the shock-phase, but sometimes falls even below normal, in the stage of resistance. The initial hyperphosphatemia may be due to the liberation of phosphorus from catabolized tissues During recovery from shock there is phosphaturia

The BLOOD VOLUME is greatly diminished in the shock-phase, but rises to or above normal during the counter-shock-phase. It tends to remain high during the stage of resistance.

DIURESIS is diminished in the shock-phase, but rises above normal during recovery.

The BLOOD pH has not yet been adequately studied throughout the course of the adaptation-syndrome, but preliminary observations indicate that there is a tendency towards acidosis during the shock-phase, this being followed by an "alkaline wave."

Other Metabolites. — ENZYMATIC ACTIVITIES probably play an important rôle in the catabolic phenomena of the alarm reaction. Following burns or trauma the peptidase activity rises abruptly in the lymph draining from the affected area; and cellular injury tends to cause a local increase in proteolytic activity, often accompanied by a rise in blood-proteases. The fibrinolysin content of the blood rises rapidly, even under the influence of comparatively mild stresses (e g., emotional upsets).

The ASCORBIC ACID content of various tissues and especially that of the adrenal cortex, markedly decreases during the alarm reaction, returning towards normal in the stage of resistance. The alleged beneficial effect of ascorbic acid in various conditions of stress is perhaps related to this phenomenon.

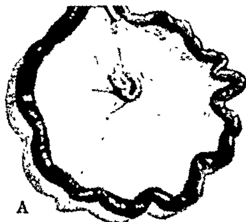
The effects of the general-adaptation-syndrome on HORMONE METABOLISM will be discussed below in connection with the endocrine theory of this syndrome. (See. p. 856)

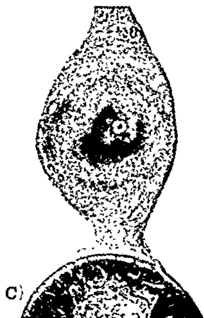
FUNCTIONAL AND MORPHOLOGIC CHANGES DURING THE GENERAL-ADAPTATION-SYNDROME

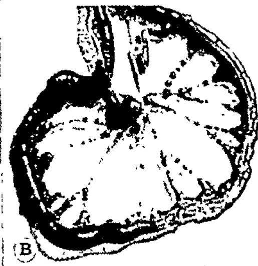
State. — Probably the most important functional consequence of the general-adaptation-syndrome is the change in resistance to stress as outlined on pp 837-838.

It is especially significant that even a fully inured organism cannot indefinitely maintain its adaptation under continuous exposure to severe stress. It is this observation which led to the concept of "adaptation energy." Apparently under the influence of prolonged adaptive work, the adaptability or "adaptation energy" of the organism is eventually exhausted. We designate the time at which this break-down of

are evident only in animals maintained on a high-sodium high-protein diet and sensitized by unilateral nephrectomy. The cardiovascular lesions are accompanied by an increase in the size of the adrenal cortex with signs of hyperactivity. Since similar lesions can be produced by corticotrophic anterior-lobe extracts and even by synthetic mineralo-corticoids (e g . desoxycorticosterone), it has been concluded that the cardiovascular lesions and the hypertension sometimes observed during the resistant phase of the general-adaptation-syndrome are due to an increase or unbalanced overproduction of mineralo-corticoids. They would thus have to be regarded as a special type of hy-









mesenteric insertion on intestinal wall Note thickening and infiltration of the transversely sectioned mesenteric arteries — D Mesenteric periarteritis nodosa produced by desoxycorticosterone overdosage in the rat Transverse section through mesenteric artery, showing final stages of periarteritis nodosa Note thick layer of hyalinized fibrin lining the vascular lumen The vessel walls have undergone partial necrosis and hence appear somewhat homogeneous

(After H Selye J. Clin Endocrinol 6, 117 1946)

corticotrophin or gluco-corticoids, on the other hand, can cause lymphopenia and eosinopenia (in animals and man) even in the absence of stress. Because of this antagonistic interplay between the medullary and cortical hormones — both of which are secreted during stress — the lymphocyte response during the alarm reaction is often biphasic.

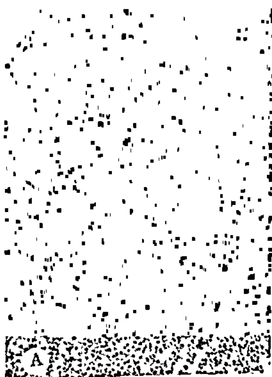
	Normal	*Alarmed*
Total white-cell count	13 000	25 000
% Polymorphs	35	76
% Lymphocytes	62	24
% Eosinophils	3	0

Average white cell count in alarm reaction synoptically summarized from various experiments on the rat. (Harlow, C. M. and H. Selye: *The Blood Picture in the Alarm Reaction*. Proc. Soc. Exper. Biol. and Med. *36*, 141 (1937). Dalton, A. J. and Selye: *The Blood Picture during the Alarm Reaction*. Folia Haematologica *62*, 397 (1939).)

The RED-CELL-COUNT and the HEMATOCRIT values are increased during the shock-phase, presumably as a result of hemoconcentration and discharge into the circulation of red-cells from the spleen and the bone marrow. During the resistant phase, there is a tendency towards blood dilution and an increase in the blood volume.

Cardiovascular System. — Under normal conditions, no typical morphologic changes occur in the heart and vessels during the general-adaptation-syndrome. The pronounced cardiovascular lesions which occur under special conditions are apparently not due to adaptation as such, but rather to maladaptation.

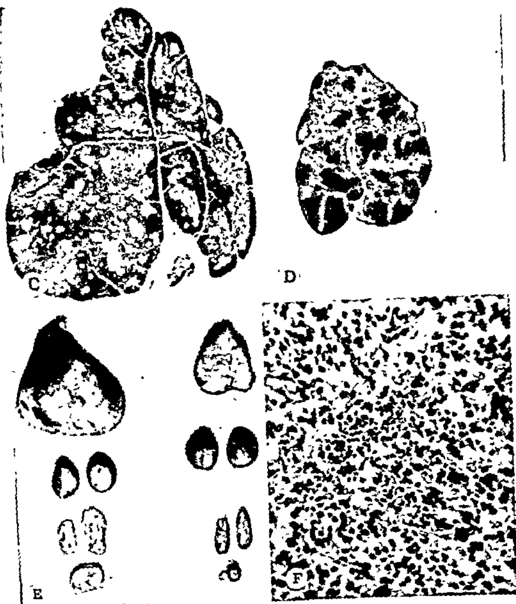
Continuous exposure to certain types of stress (e.g., cold) causes hypertension, periarteritis nodosa, hyalinization and inflammation of the renal arterioles, formation of fibrous nodules in the heart (which resemble the Aschoff nodules of rheumatic fever) and hypertension in the rat. But all these lesions





Nephrosclerosis produced by corticoids. — A. Normal kidney — medium magnification of a section through the kidney of a normal rat. — B. Experimental nephrosclerosis produced by desoxycorticosterone acetate overdosage in the rat. Note greatly enlarged glomerulus with transudation of hyaline material into the capsular space and dilated convoluted tubules, many of which contain hyaline casts. A medium sized arteriole (arrow) shows hyaline necrosis of its walls.

(After H. Selye: J. Clin. Endocrinol. 6, 117, 1946.)



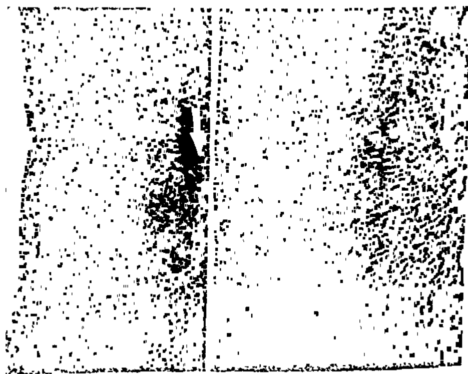
Adrenals and lymphatic organs. (cont'd.) — C. Normal thymus low magnification of a cross-section through the thymus of a normal rat Note the light medulla and dark cortical areas. The color of the latter is due to the presence of numerous thymocytes — D. Thymus in alarm reaction — cross-section through the thymus of a rat (similar to that shown in Fig C.) which received toxic doses of formaldehyde during 48 hours Note the inversion of the thymus pattern due to depletion of the cortex of thymocytes and migration of thymocyte debris into the medulla — E. Naked eye view of adrenal and lymphatic organs of normal rat and during the alarm reaction — the thymus (top), two adrenals (middle) and three iliac lymph nodes (bottom) of the normal animal (left), whose thymus is shown in Fig C. and of the animal during the alarm reaction (right), whose thymus is shown in Fig D Note the marked decrease in thymus and lymph node size as well as the increase in adrenal size, accompanied by loss of cortical lipids (brown macroscopic appearance) in the animal killed during the alarm reaction — F. Thymus in alarm reaction — higher magnification of an area in the medulla of the thymus shown in Fig D. Note the well developed epithelioid thymic reticulum with granular dark thymocyte nuclear debris These degenerated thymocyte nuclei migrate towards the medulla and are eventually taken up by the thymic lymphatics

(After H Selye J Clin Endocrinol 6 117 1946)

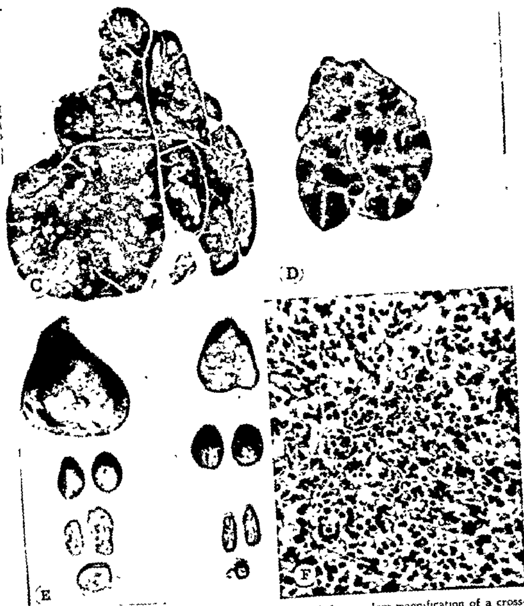
percorticoidism, due to an abnormal defensive hyperactivity of the adrenal cortex and would represent diseases of adaptation. (Cf. pp. 858-866.)

We do not yet know why both in animals and in man, continuous stress produces cardiovascular lesions only under certain conditions. It is possible that the disproportionate increase in mineralo-corticoids, rather than in the other cortical hormones is responsible for the lesions in certain cases, but this has not been proven. Since the mineralo-corticoids are conditionally-acting hormones, it is more probable that their damaging effect upon the cardiovascular system depends upon the diet (especially the sodium chloride intake), hereditary predisposition and other sensitizing factors. This view is supported by numerous observations indicating that, in animals, even exogenously administered corticotrophin or corticoid hormones cause cardiovascular damage only on certain diets and that some species are genetically much more predisposed to corticoid intoxication than others. In human pathology it is quite possible that incidental metabolic derangements occasioned by continued exposure to stress (infections, intoxications, nervous stimuli, etc.) may sensitize or desensitize the cardiovascular system to the excess of mineralo-corticoids produced under the influence of the general-adaptation-syndrome.

Lymphatic System. — The THYMUS undergoes conspicuous "accidental involution" during the alarm reaction. This is obviously due to an increased cortical-hormone production, since it is prevented by hypophysectomy or adrenalectomy, but can be elicited even in the absence of the hypophysis or



Adrenals and lymphatic organs during the alarm reaction. — A. Normal adrenal — section through the adrenal cortex of a normal rat Note width of cortex (delimited by arrows) and clearcut differences between the zona glomerularis and fasciculata — B. Adrenal in alarm reaction — section through the adrenal cortex of a rat (similar to that shown in Fig A.) which received toxic doses of formaldehyde, subcutaneously during 48 hours Note greater width of the cortex, whose cells lost their light, lipid granules The border between fasciculata and reticularis is no longer distinct (Cont'd)



Adrenals and lymphatic organs. (cont'd.) — **C.** Normal thymus, low magnification of a cross-section through the thymus of a normal rat. Note the light medulla and dark cortical areas. The color of the latter is due to the presence of numerous thymocytes. — **D.** Thymus in alarm reaction — cross-section through the thymus of a rat (similar to that shown in Fig. C.), which received toxic doses of formaldehyde during 48 hours. Note the "inversion of the thymus pattern" due to depletion of the cortex of thymocytes and migration of thymocyte debris into the medulla. — **E.** Naked eye view of adrenal and lymphatic organs of normal rat and during the alarm reaction — the thymus (top), two adrenals (middle) and three iliac lymph nodes (bottom) of the normal animal (left) whose thymus is shown in Fig. C, and of the animal during the alarm reaction (right), whose thymus is shown in Fig. D. Note the marked decrease in thymus and lymph node size as well as the increase in adrenal size, accompanied by loss of cortical lipids (brown macroscopic appearance) in the animal killed during the alarm reaction. — **F.** Thymus in alarm reaction — higher magnification of an area in the medulla of the thymus shown in Fig. D. Note the well developed epitheliod thymic reticulum with granular, dark thymocyte nuclear debris. These degenerated thymocyte nuclei migrate towards the medulla and are eventually taken up by the thymic lymphatics.

(After H. Selye, J. Clin. Endocrinol. 6: 117, 1946.)

adrenals if adequate doses of corticoids are administered.

The loss of thymus weight is preceded by histologic signs of nuclear pyknosis with consequent complete dissolution of thymocytes. Large macrophages engulf the dead thymus cells and carry them away through the lymphatics. At the same time, the thymic reticulum reverts to its original epithelial type, inasmuch as its cells become roundish or polygonal and rich in cytoplasm In the reticulum there often appear massive cell nests resembling parathyroid tissue, new Hassall bodies, or colloid-filled vesicles similar to those of the thyroid. When involution is most acute the entire organ is distended with jelly-like edema and small petechial hemorrhages may occur. During the resistant stage the thymus tends to revert toward normal, but in the stage of exhaustion it again undergoes severe involution

The LYMPH NODES, SPLEEN AND OTHER LYMPHATIC ORGANS are less markedly affected than the thymus, but may undergo essentially similar involutional changes, especially in the germinal centers. Simultaneously there is marked proliferation of the macrophages throughout the RETICULOENDOTHELIAL SYSTEM and especially in the lung The ability of these cells to phagocytose intravenously injected particles (e g., india ink) is enormously increased This may be of use in the defense against bacterial invasion

Respiratory System. — Pleural transudates or hyperemia of the LUNGS, often accompanied by edema and even acute pneumonia, may occur during the alarm reaction, but these changes are inconstant.

Digestive System. — GASTROINTESTINAL ULCERS are characteristic of the shock-phase. They are most frequent in the stomach and small intestine and are usually accompanied by more or less severe hemorrhage into the lumen. These are merely signs of damage and occur, even more readily than usual in adrenalectomized animals which are unable to develop an effective countershock. These ulcers are probably comparable to the acute gastrointestinal erosions frequently observed during shock in man, where they account for the dark, coffee-colored vomitus seen under such conditions. They often develop following burns (Curling's ulcers) or intense emotional excitement (e g., "Air-raid ulcers").

In case of particularly acute and severe damage, that part of the cecum which in the rat corresponds to the human appendix, may be specifically affected and show marked hemorrhagic edema, similar to that observed during the first stages of acute APPENDICITIS. It is possible that perhaps certain cases of cryptogenic acute appendicitis in man may also be due to similar systemic, rather than local, causes.

The LIVER often shows only signs of cloudy swelling and a decrease in size. The latter may be partly accounted for by the decrease in blood-volume and partly by protein-catabolism. More extensive atrophy, with marked degenerative changes, focal necrosis and intense fatty infiltration are but rarely seen during the alarm reaction.

The so-called "HIBERNATING GLAND" ("interscapular gland" or "brown fat") is a special kind of adipose tissue, especially well developed between the shoulder blades in the rat. It also occurs around the kidney and along the vertebrae, in the retroperitoneal and retropleural space in man. Discharge of lipids, intense hyperemia and edema of this tissue is a particularly early and sensitive indicator of tissue catabolism during the alarm reaction, especially in the rat.

The PANCREAS likewise undergoes acute involution during the alarm reaction This affects mainly the acinous tissue whose cells discharge their zymogen granules, decrease in size and may even become necrotic. It is possible

that the acute pancreatitis occasionally seen in man after burns and other types of sudden stress is related to this phenomenon. The Langerhans islets remain essentially normal although they may reveal increased nuclear pyknosis and mitotic proliferation

Urinary System. — The KIDNEY reveals no very characteristic changes during the general-adaptation-syndrome under normal conditions As in the cardiovascular system (see p 846) the response depends largely upon the diet, genetic predisposition and the specific nature of the eliciting damaging agent The nephrosclerosis (and sometimes even acute nephritis) seen in the course of the general-adaptation-syndrome, is almost invariably accompanied by hypertension and cardiovascular lesions, similar to those described above The production of both the



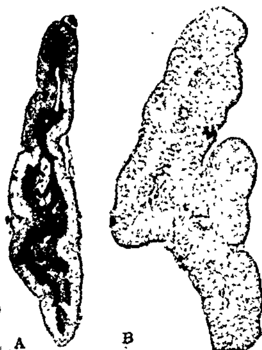




Nephrosclerosis produced by anterior-pituitary extract. — A. Experimental nephrosclerosis produced with lyophilized anterior-pituitary material and high NaCl intake in the rat. Note greatly dilated tubules, some with casts and transudation of hyaline material into capsular space — B Experimental nephrosclerosis — another area of the kidney shown in Fig A Note hyalinization of afferent arteriole, near its junction with glomerulus (arrow), enormously enlarged glomerulus with transudation of hyaline material into capsular space. — C. Prevention of experimental nephrosclerosis with NH_4Cl — The rat whose kidney is shown here, was treated in the same manner as that whose kidney is represented in Fig A and B, however, it was simultaneously given NH_4Cl solution to drink Compare size of glomeruli and note that pathologic changes are completely prevented (After H Selye J Clin Endocrinol 6 117 1946)

renal and cardiovascular changes is facilitated by unilateral nephrectomy, high-protein or high-sodium diets, and is inhibited by the administration of acidifying salts (e.g., NH_4Cl). These renal lesions are apparently also phenomena of mal-adaptation, rather than of adaptation, being due to endogenous intoxication with mineralo-corticoids under conditions favorable for the manifestation of their toxicity.

Endocrine Organs. — The ADRENAL CORTEX displays especially pronounced changes during the general-adaptation-syndrome In the *alarm reaction* its individual cells hypertrophy and discharge their lipid, cholesterol and ascorbic acid granules. At the same time, there is also a loss of the histochemically demonstrable "plasmal" and "ketosteroid" granules All these changes have



Adrenal-cortical enlargement in severe hypertension. — A. Cross-section through the adrenal of a normal adult man — B. Cross-section through the adrenal of a 64-year-old man, who suffered from severe hypertensive cardio-renal disease with terminal pulmonary embolus and thrombosis of a cerebral artery. Note great enlargement of the adrenal cortex, while the medulla remained essentially normal

(Courtesy of Dr E von Haam)

been interpreted as signs of increased endocrine activity. True hyperplasia (cell multiplication) is less pronounced, indeed usually cell-disintegration (holocrine secretion ?) prevails. It is especially noteworthy that the discharge of sudanophilic lipids (unlike that of the ascorbic acid and cholesterol granules) is difficult to duplicate with corticotrophin. It has been assumed that a special "degranulation factor" is produced during the shock-phase of the alarm reaction and that both corticotrophin and this factor are required to elicit a discharge of sudanophilic lipids from the cortex. All the above mentioned changes take place during the first hours of the alarm reaction, and do not reach their peak until the counter-shock phenomena become evident.

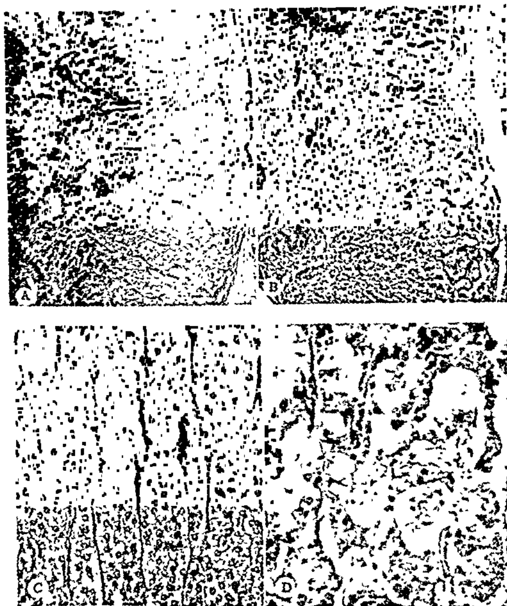
During the *stage of resistance*, the weight of the adrenal cortex remains high, but lipids, cholesterol, ascorbic acid and other storage products, discharged during the alarm reaction, reappear and indeed may become excessively plentiful in the adrenal cortex. It is well to keep in mind that the adrenal concentration of all these storage products does not necessarily run parallel. For instance, if the stress is fairly severe, the ascorbic acid may remain low in the stage of resistance although the sudanophilic lipids (and to a lesser extent the cholesterol granules) are abundant.

During the *stage of exhaustion*, the cortex resembles that of the alarm reaction, but frequently there are hemorrhages and round cell infiltrations with extensive necrosis and degenerative phenomena These are sometimes interpreted as due to an adrenal breakdown caused by overwork.

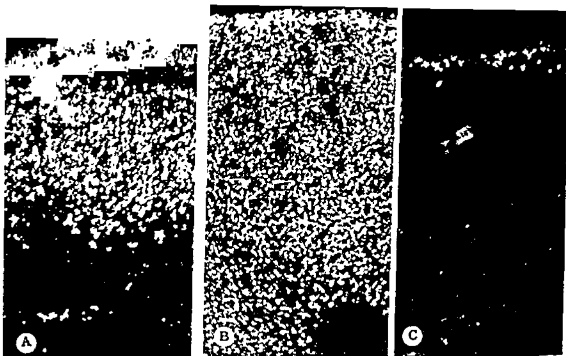
In man, the adrenal changes during the adaptation-syndrome are essentially similar to those seen in animals. It has been claimed, however, that degenerative changes, reminiscent of postmortal autolysis, are more frequent in

patients who died during the alarm reaction than otherwise. Furthermore, in patients dying from acute stress, the cortical cells tend to rearrange themselves and form tubule-like structures, the center of which is filled by degenerating cells

The bright yellow (lipid-rich), thick adrenal cortex, frequently seen in patients who have died from hyperten-



Adrenals during alarm reaction (Man). — A. Low magnification of normal adrenal cortex from a 24 year old man who died from an accident Note uniformity of fat-filled (light) cells in outer cortex — B. Adrenal during alarm reaction due to very severe diphtheria which resulted in death on 7th day Note characteristic pattern in outer cortex The peripheral dark cells are lipid free and surround the fat-filled degenerating central cells Similar changes have been noted following a variety of infections, intoxications and traumatic injuries in man — C. Higher magnification of A — D Higher magnification of B The degenerating fat-filled cells in the center of the tubules have often been interpreted as due to postmortal autolysis, but are now regarded as characteristic of the response to stress (Courtesy of Dr N Zamcbek)



Birefringent material in adrenal cortex during the general-adaptation-syndrome. — A. Adrenal cortex of a normal control rat as seen under the polarizing microscope. Note large amounts of birefringent lipid both in the zona glomerulosa and in the outer fasciculata, none in the [illegible] B. Great in- [illegible] from the adrenals during the exhaustion phase of the general-adaptation- [illegible] only the glomerulosa contains birefringent granules Essentially similar lipid depletion is seen in the alarm-reaction phase In this instance the general-adaptation-syndrome was produced by pantothenic-acid deficiency (Courtesy of Drs H W Deane and G M McKibbin)

sion is reminiscent of that observed in animals during the stage of resistance.

Hypophysectomy prevents the development of the adrenal-cortical changes during the general-adaptation-syndrome, but has no effect upon the adrenaline discharge by the medulla.

If, during the resistant stage to one *type of stress, the organism is exposed to a different alarming stimulus,* the lipid, cholesterol and ascorbic acid granules of the adrenal cortex are again discharged.

The chromaffin granules of the MEDULLA are discharged and the medullary cells become vacuolized within the first few minutes after exposure to an alarming stimulus. Since this response can be prevented by splanchnicotomy it is probably mediated through the sympathetic nervous system.

In both sexes the GONADS undergo atrophy during the general-adaptation-syndrome This has also been interpreted as due to the "shift in pituitary-hormone production," which necessitates a decreased secretion of other hypophyseal principles in order to permit maximal corticotrophin elaboration (see p 845) Sterility (in either sex) and the estrus or menstrual anomalies resulting from continuous exposure to stress, are probably also due to this same shift"

The anterior-lobe of the HYPOPHYSIS often shows degranulation, especially of the eosinophils, and sometimes there are waves of nuclear pyknosis In the rat, hypertrophy and hyperplasia of the basophils is induced by chronic exposure to various types of stress, and this change may be the morphologic basis for the increased corticotrophic hormone production in the general-adaptation-syndrome

The THYROID may display signs of atrophy and involution during the early stages, but this is sometimes followed by hyperplasia during the stage of resistance It has been claimed that the thyroid-stimulating effect of various

CHANGE \ STAGE		ALARM REACTION: Shock phase	ALARM REACTION: Counter-shock phase	STAGE OF RESISTANCE	STAGE OF EXHAUSTION
Resistance	Specific	—	+ +	+ + +	— — —
	Crossed	—	+	— — —	— — —
Body weight		—	—	— or N	— — —
Diuresis		—	+	+	—
Blood Volume		— —	+ or N	+	— —
Blood Sugar		+ +	—	+ or N	— —
Blood Chlorides		—	— —	+ or N	— or N
Blood Fibrinogen		+	+ +	+ or N	?
Blood N P N		+	+ +	N	+ +
Uric acid in Blood and Urine		+	+ +	?	?
Leucocyte Count	Polymorphs	+	+ +	?	?
	Lymphocytes	+	— —	?	?
	Eosinophils	+	— — —	?	?
Sedimentation rate		+	+ +	?	?
Adrenal	Size	— or N	+ + +	+ +	?
	Cortical lipids	—	— — —	+ + +	+ + +
	Medullary Chromaffinity	—	— —	N	— —
Thymus and Lymphatic Tissue		—	— —	—	—
Kidney		N	Tubular hypertrophy	*Nephrosclerosis	— — —
Blood Vessels		Capillary damage	Capillary damage	*Arteriosclerosis (hyalinization)	*Nephrosclerosis
Heart		Tachycardia	Tachycardia	*Myocarditis, Aschoff nodules	*Arteriosclerosis (fibrosis)
Gastroint Tract		Hyperemia	Ulcers	N	*Myocarditis Aschoff nodules
Gonads ♂ + ♀ Sexual cycle ♀		N	—	— —	Ulcers
					— — —

+ = increased
— = decreased
N = normal unchanged
* = changes in these organs are largely dependent upon sensitization (Na partial nephrectomy)
? = available data are not conclusive

Nomenclature and symptomatology of the general-adaptation-syndrome. Schematic representation of the most prominent morphologic and metabolic changes during the general-adaptation-syndrome and the diseases of adaptation

non-specific toxic substances and the development of Graves' disease after sudden (often emotional) stress may be the consequences of abnormal adaptive reactions

THEORETIC INTERPRETATION OF THE GENERAL-ADAPTATION-SYNDROME

A. — Theories Concerning the Shock-Phase. — The greatest problem in interpreting the manifestations of shock is to explain why so many different agents lead to essentially the same syndrome and through what channels an injury to a limited part of the body can affect the entire organism. Many theories have been proposed in an effort to explain these two basic problems, among them, we might mention the following

(1) Impaired circulation

(2) Dehydration and hemoconcentration

(3) Endogenous intoxication with various metabolites

(4) Nervous disturbances

(5) Disturbed thermoregulation

(6) Hypochloremia.

(7) Deficiency in some important metabolite, perhaps the corticoid hormones themselves, due to increased consumption or increased need (relative insufficiency) for such substances

None of these theories have been fully proven but it is highly probable that a state of relative corticoid insufficiency exists during stress This relative lack of corticoids may in itself (through some phenomenon, similar to that which causes compensatory hypertrophy) increase the corticotrophin production of the pituitary and thus initiate a defense reaction.

B. — Theories Concerning the Entire General-Adaptation-Syndrome. — The hypothesis of ADAPTATION ENERGY is based on the following observations: General resistance rises in the counter-shock-phase of the alarm reaction, which intimates that the "adaptability" of the organism is "mobilized" in some manner On the other hand, following prolonged exposure to stress (that is, during the resistant stage of the general-adaptation-syndrome) when the organism has acquired a high degree of adaptation to the agent to which it had been exposed, *it becomes especially irresistant, and* unable to adapt itself, to other damaging stimuli. This suggested that the body may possess only a limited amount of "adaptability" or "adaptation energy," which is consumed while adaptation is acquired to a certain agent, so that less of it remains available for resistance against other types of stress. Even continued treatment with the same agent (which originally caused an *alarm reaction and to which the organism* became adapted), eventually becomes damaging again ("stage of exhaustion" of the general-adaptation-syndrome). It would be extremely difficult to explain such a loss of acquired adaptation without assuming, that due to continued "use," all the available adaptation energy of the organism had been exhausted.

To quote but one possible clinical *application* of this hypothesis, we may call attention to the fact that aviators who had to adapt themselves to work under nervous tension at high altitudes, often break down following a period of apparently complete inurement. This break-down is characterized, among other things, by gastrointestinal disturbances and other manifestations reminiscent of the "stage of exhaustion" of the general-adaptation-syndrome. In such cases it has been customary to speak of "exhaustion of the nervous energy reserve."

The adaptation energy hypothesis can not attempt to explain the pathogenic mechanisms responsible for the development of the adaptation-syndrome. *It is merely outlined as a working hypothesis* which may help to visualize the fact that adaptation to a variety of stresses occurs in three distinct stages.

The FUNCTIONAL, MAINLY HORMONAL, INTERRELATIONS between the various organs affected by the general-adaptation-syndrome are much better understood. An attempt is made to summarize the most important among *these in the drawing on p. 857.*

It will be noted that STRESS initiates the entire chain of reactions. It appears to act upon the organism through two distinct pathways. The manifestations of damage (clinical "shock", loss of body weight and nitrogen, gastrointestinal ulcers, transitory hyperkalemia and hypochloremia) are mediated through *unidentified pathways* (nervous stimuli ?, deficiencies ?, toxic metabolites ?), *but certainly not through the* hypophyseo-adrenal defense mechanism They are not manifestations of defense, but rather of defencelessness. They are not prevented, but rather aggravated by hypophysectomy or adrenalectomy.

Secondly, again through unidentified pathways and perhaps through the above-mentioned blood-borne tissue-catabolites, stress sets into action the hypophyseo-adrenal defense mechanism. It first acts upon the HYPOPHYSIS causing it to increase *corticotrophin* production at the expense of a decreased elaboration of gonadotrophins, luteotrophin, growth hormone, etc. This leads to an *inhibition of somatic growth,* involution

STRESS
SOMATIC GROWTH
HYPOPHYSIS
MAMMARY GLAND
TESTIS
ADRENAL CORTEX
OVARY
LYMPHATIC ORGANS
BLOOD COUNT
ORGANIC METABOLISM
RPS
KIDNEY
HEART
VESSELS
BLOOD-PRESSURE

Functional interrelations during the general-adaptation-syndrome. Schematic drawing illustrating the working hypothesis which appears to be most readily compatible with pertinent observations made up-to-date. RPS (renal-pressor-substances) stands for renin and other vasoconstrictors (e.g., pressor amines). It appears that corticoids increase their production and simultaneously decrease their normal inactivation by the kidney. Note that actions of cortex on lymphatic organs and organic metabolism are due to gluco-corticoids, other effects shown here to mineralo-corticoids. Although a high blood-pressure greatly facilitates the production of organic cardiovascular changes (as indicated here) the vasopressor effect of renal hormone(s) is exerted upon the vessels directly (even in vitro). The mineralo-corticoids probably produce organic cardiovascular changes largely, if not entirely, because they augment renal-pressor-substance production, but a direct effect (shown here) may also play a rôle.

of the gonads and — if the reaction occurs during lactation — to cessation of milk secretion. It is this change in the type of pituitary hormones produced, which is referred to as the "shift in hypophyseal hormone production."

The rise in corticotrophin secretion causes enlargement of the ADRENAL CORTEX with signs of increased corticoid production. These corticoids in turn elicit changes in organic (gluco-corticoids) and inorganic (mineralo-corticoids) *metabolism* as well as atrophy of the THYMUS AND OTHER LYMPHATIC TISSUES.

At present, it is not quite clear whether corticoids destroy the circulating lymphocytes directly, or whether they influence the lymphocyte-count merely by diminishing lymphocyte formation in lymphatic organs. Perhaps both these mechanisms are operative. It has been suggested, but not proven, that globulins, useful in the formation of antibodies are produced during stress, due to the action of corticoids on the thymico-lymphatic apparatus, inasmuch as these globulins come from the bodies of disintegrating lymphocytes.

That stress actually affects the adrenal cortex through the hypophysis has been proven in experiments on hypophysectomized animals, in which stress has no effect either upon the adrenal cortex or upon any other organ indicated on the graph, below the level of the hypophysis — correspondingly, adrenalectomy prevents the effect of either stress or hypophyseal extracts upon the organs shown below the level of the adrenal; administration of corticoids can affect these terminal target organs directly, irrespective of the pres-

ence or absence of the hypophysis and adrenal cortex.

It is somewhat more problematic how the corticoids affect the cardiovascular apparatus, the kidney, the joints and the blood-pressure. Presumably, stimulation of α_2-*globulin* production by the *liver* is part of their action on organic metabolism. At the same time the increased *gluconeogenesis* provides more readily combustible energy by raising the glycogen stores and the blood sugar. This is certainly also a useful defense reaction.

The effect of mineralo-corticoids upon the KIDNEY (nephrosclerosis) is probably dependent upon their action on *electrolyte metabolism* (sodium retention), since withdrawal of sodium inhibits this effect and purified gluco-corticoids cause no nephrosclerosis. The nephrosclerotic kidney presumably produces an increased amount of renin, due to obstruction of blood-flow through the glomerular tufts. This *renin* acts upon the *hypertensinogen* (α_2-globulin) of the blood, to produce *hypertensin*, a pressor substance It is possible, however, that *other renal pressor substances* are also involved They are presumably produced by the *spiral segments* of the proximal convoluted tubules. Treatment with desoxycorticosterone causes hypertrophy of the cells in these segments and hypertension, much before there is any nephrosclerosis. Later, however, when the sclerosis of the renal vessels becomes manifest, there arises a vicious circle inasmuch as nephrosclerosis aggravates hypertension and hypertension increases nephrosclerosis

Recent observations suggest that the tubular damage caused by mineralo-corticoids can interfere with the normal inactivation of renal pressor substances. Furthermore, the regulation of the blood volume by the kidney can be deranged by overdosage with these corticoids, especially if the Na intake is high. It appears to depend largely upon experimental conditions, which of these factors, plays the major rôle in the causation of hypertensive diseases.

Presumably the increased *blood pressure* (perhaps in conjunction with direct toxic actions of Na and/or renal pressor substances) causes changes in the HEART (infarcts, Aschoff? nodules) and the BLOOD-VESSELS (periarteritis nodosa)

We have no explanation for the production of JOINT lesions (polyarthritis) which is occasionally seen under the influence of mineralo-corticoids or impure pituitary extracts. It is probable, however, that the beneficial effect of gluco-corticoids and corticotrophin upon rheumatoid arthritis, is somehow related to this arthrotropic action of corticoids.

CLINICAL IMPLICATIONS OF THE GENERAL-ADAPTATION-SYNDROME

Adaptation to our surroundings is one of the most important physiologic reactions in life, one might perhaps even go so far as to say that the capacity of adjustment to external stimuli is the most characteristic feature of living matter It is not unexpected, therefore, that some of the most common diseases of man appear to be diseases of the adaptive mechanism. There is increasingly more evidence to show that the diseases of adaptation play the same important rôle in pathology as the general - adaptation - syndrome in physiology

The maladies which should be considered as possibly belonging to the group of the "diseases of adaptation" are the following ·

Hypertension and "hypertensive diseases". — Since under certain conditions hypertension can be produced experimentally in animals by continued exposure to stress, it is reasonable to assume that spontaneous hypertensive disease in man may also occur as a result of chronic exposure to non-specific damaging agents. In such cases it is likely that stress causes an increased

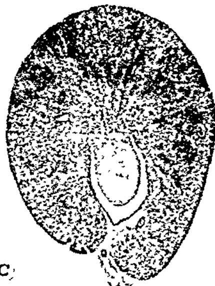
corticotrophin production by the anterior-lobe and this in turn stimulates the corticoid hormone production of the adrenals; the resulting hypertension and nephrosclerosis could then be due to an endogenous intoxication with the organism's own corticoids. Not every *kind of damage is equally prone to raise the blood pressure through this mechanism.* Various types of *stress* elicit different degrees of corticoid hormone over-production and perhaps some stimulate gluco-corticoid rather than mineralo-corticoid secretion; only the latter causing nephrosclerosis with hypertension. Furthermore, hypertension would not result if the metabolic changes elicited by the stress created unfavorable conditions for the development of corticoid intoxication. The previously *mentioned observation that diets poor* in sodium and protein or the production of *acidosis (through the administration* of NH_4Cl or other "acidifying salts") counteracts the toxicity of corticotrophins, clearly indicates that the damag-



The endocrine kidney —A. Macroscopic view of heart, aorta, kidney and adrenals of a rat. In this animal the aorta was *partially ligated between origin of 2 renal arteries* (lower arrow) and LAP treatment was given during 14 days. Note great enlargement of heart, adrenals and right kidney. Heart contained *macroscopically visible* Aschoff (?) nodules, kidney surface is irregular, (beginning nephrosclerosis), adrenals are dark (hyperemia and discharge of lipid granules) *and there are several periarteritic nodules on superior* mesenteric artery (upper arrow). Aorta is thickened but only in section above partial ligature. Left kidney, whose artery *originates below ligature, is subnormal in size but* entirely free of nephrosclerotic nodules. — B. Cross-section through left kidney of rat shown in A. Note great decrease *in kidney size, mainly due to involution of medulla.* Cortex is almost as wide as in normal kidney; small decrease in width of the renal cortex is readily accounted for by dis*appearance of nephronic lumina and partial collapse of* glomeruli. Renal pattern is very regular, *showing* no trace of nephrosclerosis. — C. Cross-section through right kidney *of rat shown in A. Note irregularity of pattern due to* patchy nephrosclerosis. (Same magnification as Fig. B.)
(After H. Selye and H. Stone, J. of Urology 56: 399, 1946.)



B



C

ence or absence of the hypophysis and adrenal cortex.

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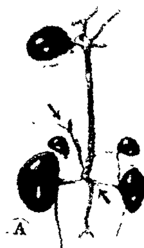
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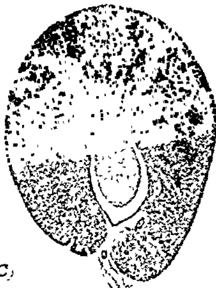
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The endocrine kidney. —A. Macroscopic view of heart, aorta, kidney and adrenals of a rat. In this animal the aorta was partially ligated between origin of 2 renal arteries (lower arrow) and LAP treatment was given during 14 days. Note great enlargement of heart, adrenals and right kidney. Heart contained macroscopically visible Aschoff (?) nodules, kidney surface is irregular, (beginning nephrosclerosis), adrenals are dark (hyperemia and discharge of lipid granules) and there are several periarteritic nodules on superior mesenteric artery (upper arrow). Aorta is thickened but only in section above partial ligature. Left kidney, whose artery originates below ligature, is subnormal in size but entirely free of nephrosclerotic nodules. — B. Cross-section through left kidney of rat shown in A. Note great decrease in kidney size, mainly due to involution of medulla. Cortex is almost as wide as in normal kidney; small decrease in width of the renal cortex is readily accounted for by disappearance of nephronic lumina and partial collapse of glomeruli. Renal pattern is very regular, showing no trace of nephrosclerosis. — C. Cross-section through right kidney of rat shown in A. Note irregularity of pattern, due to patchy nephrosclerosis. (Same magnification as Fig. B.)

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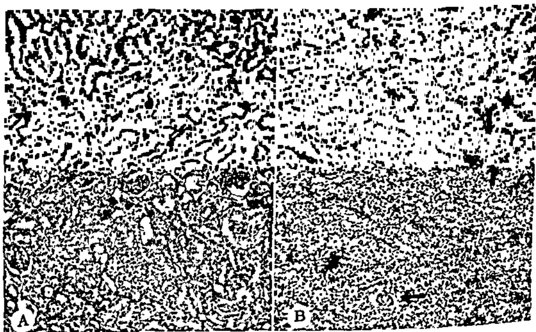
ing action of the latter is conditional upon the state of metabolism as a whole.

Periarteritis Nodosa. — In animals chronically treated with desoxycorticosterone, and in sensitized (unilaterally nephrectomized, high sodium and high protein diet) animals exposed to certain types of stress (e.g., cold), diffuse periarteritis nodosa develops, especially in the mesenteric, cardiac and brain vessels. Histologically, this periarteritis nodosa is so similar to the intrarenal vascular lesions of malignant nephrosclerosis that it is tempting to assume that nephrosclerosis and periarteritis nodosa are both results of the same pathogenic mechanism.

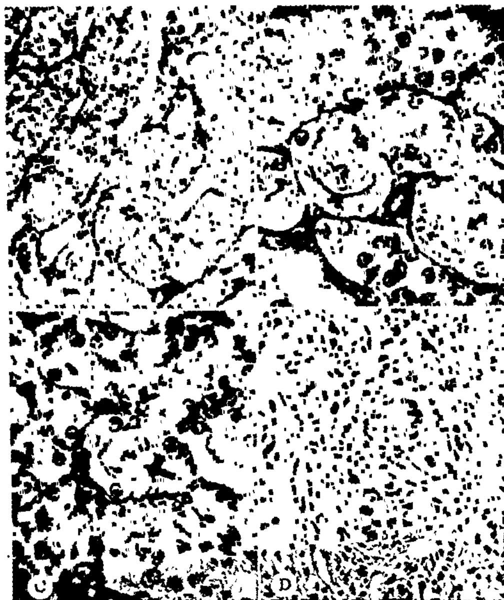
Spontaneous periarteritis nodosa is often seen in man as a sequel of acute rheumatic fever. It has even been considered to be a type of "rheumatic arteritis," and exhibits the same histologic characteristics and the same distribution in the various vascular territories as the experimental form produced by corticoids. It is probable therefore, that periarteritis nodosa likewise belongs to the diseases of adaptation caused by abnormal adrenal-cortical hyperactivity.

It is doubtful whether *arteriosclerosis* merely represents a particularly chronic form of essentially the same vascular lesions as are found in periarteritis nodosa. Since arteriosclerosis also tends to occur in individuals exposed to continuous stress and is likewise accompanied by hypertension, there may be some relationship between these two types of vascular lesions.

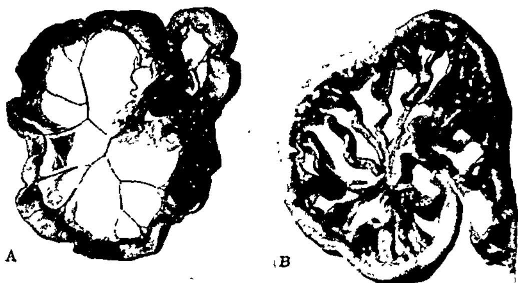
Nephrosclerosis. — The facts mentioned above in connection with hypertension are equally applicable to nephrosclerosis, hence we need not repeat them here. It is evident that under the influence of the vascular lesions produced by corticoids, the lumina of the renal arterioles are greatly reduced;



The endocrine kidney. — **A.** High magnification of an area from normal control kidney — **B.** High magnification of an area from left "endocrine kidney" of a rat whose aorta was partially ligated between origins of two renal arteries. Note that all tubular lumina and Bowman's capsule spaces have disappeared. Glomeruli tend to melt in with *tubular* parenchyme but are still distinguishable in places (2 arrows). A small arteriole, near lower margin (1 arrow) shows no trace of hyalinization. General pattern of this kidney is reminiscent of an adrenal or parathyroid, since it consists exclusively of solid, epithelial cell cords. (Same magnification as A.) (After H. Selye and H. Stone, J. of Urology *56*: 399, 1946.)



The endocrine kidney. — A. High magnification of an area from left endocrine kidney of another LAP treated rat whose aorta was partially ligated between the two renal arteries. Note solid epithelial parenchyme, although no secretion of urine occurs and tubular lumina are absent, epithelial cells are well preserved and show no sign of degeneration or necrosis. — B. Another field of same kidney under oil immersion. Note that tubular lumina are filled *with proliferating epithelial cells. A mitotic figure (arrow) is seen in a convoluted tubule.* Note also syncytial formation near upper and lower right-hand corner and rather polymorph appearance of nuclei. — C. Another area of the kidney shown in A. Polymorph appearance of nuclei and a large mitotic figure in center of field (arrow) are clearly visible here under oil immersion. Many mitotic divisions in these kidneys clearly indicate that renotrophic stimulation is possible even in small endocrine kidney. — D. Section through a *myocardial nodule of another rat treated with LAP. Note proliferation of capillary endothelia* which tend to fuse and thus form polynuclear giant cells (arrows) similar to those seen in acute rheumatic fever. In this area, myocardial fibers have been completely replaced by granulomatous tissue. (After H. Selye and H. Stone, J. of Urology 56, 399, 1946.)



Periarteritis nodosa caused by the "Endocrine kidney." — A. A loop of small intestine in a normal control rat (body weight 120 gm.) showing the normal aspect of the mesenteric vessels — B. Pronounced thickening of all mesenteric vessels which showed the histologic characteristics of periarteritis nodosa. In this rat (body weight 125 gm.) a partially-constricting ligature had been placed, 38 days previously, on the aorta between the origins of the two renal arteries. It caused complete endocrine transformation of the left kidney, accompanied by marked hypertensive disease.

this decreases the blood pressure in the kidney, a change known to cause an increased production of pressor substance (probably renin). Thus a vicious circle results: the more the blood pressure rises, the more the lumina of the renal arterioles shrink due to the blood-vessel-damaging effect of high-blood pressure; correspondingly, the kidney continues to increase its pressor-hormone production.

In this connection it is noteworthy that constriction of the renal artery, by means of an intervention which permits a decrease in the intra-glomerular pressure to the level of the protein-osmotic pressure of the blood, abolishes urine secretion by eliminating the filtration pressure; consequently the entire kidney is transformed into purely endocrine tissue. Thus, we obtain an exclusively "endocrine kidney" which does not participate in urine formation. This morphologic transformation of one kidney is accompanied by the most acute and malignant type of nephrosclerosis in the contralateral kidney and by severe, usually fatal, hypertension. Significantly, no nephrosclerosis occurs in the kidney in which the blood pressure had been decreased; this suggests that nephrosclerosis is largely dependent upon the increase in blood pressure and not solely caused by humoral factors. Since both the endocrine and the other kidney of such test animals are perfused with the same blood, the nephrosclerosis should be equal on both sides, were it due to purely chemical stimuli. *It is* probable that, both in spontaneous and in experimental nephrosclerosis, hyalinization of certain glomeruli transforms individual nephrons into "endocrine nephrons," since such hyalinization has approximately the same effect upon the individual nephron as the operation for the production of the "endocrine-kidney" has upon the entire organ. However, mineralo-corticoids undoubtedly also possess a direct stimulating action upon the cells of the spiral segments. During desoxycorticosterone treatment, for instance, these parts of the tubules enlarge as soon as the blood-pressure

rises; much before there is any trace of an organic vessel lesion.

Nephritis. — In very acute corticoid or corticotrophin intoxication, actual inflammatory lesions have been seen in the kidney; the possibility must be considered that nephritis may be an especially acute type of the same change which causes nephrosclerosis. The frequent occurrence of nephritis during the recovery period from acute infectious diseases (e.g., scarlet fever, diphtheria) raises the possibility that the disease may be due to excessive corticoid production at a time when the defense mechanism against the infection has fully developed.

Rheumatic Diseases. — Granulomatous nodules (similar to Aschoff nodules), endocardial vegetations, pericardial transudates, and sometimes even acute joint-lesions tend to occur in animals receiving excessive amounts of mineralo-corticoids This suggested that the so-called cryptogenic rheumatic diseases may likewise represent diseases of adaptation due to endogenous corticoid intoxication. It is known that fatigue, chills, traumatic injuries, mental upset, etc., may cause the relapse of a patient with rheumatic fever from a quiescent into an acute febrile state

Here again, the main problem is to find a common pathway which could explain the similarity of the lesions produced by such a variety of agents Acceptance of the hypophyseo-adrenal theory does not necessitate abandonment of other interpretations. It merely implies that such agents as cold, microorganisms, serologic disturbances, etc., can so influence the hypophyseo-adrenal defense mechanism that an excessive amount of mineralo-corticoid hormone is elaborated whenever an individual is exposed to them; the rheumatic attack would then result from such a derailed defense mechanism.

Waterhouse-Friedrichsen Syndrome. — Acute fulminating infections, especially with meningococci may elicit a syndrome which resembles acute adrenal insufficiency and is accompanied by hyperemia and diffuse hemorrhages into an apparently hyperactive adrenal

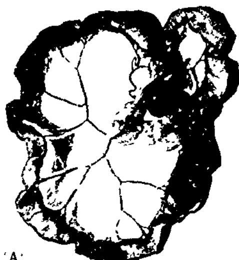
This resembles a severe alarm reaction complicated by a hemorrhagic diathesis It may be that such grave endogenous intoxication with microbial products calls for an enormously increased corticoid production, thus causing a state of relative adrenal insufficiency and eventually a breakdown of the hyperactive suprarenal, due to an inability to adjust itself to this stress The hemorrhagic diathesis appears to be due to a specific action of the pathogenic organism.

Eclampsia. — There is a striking similarity between the glomerular lesions seen in eclampsia and those produced by a variety of other non-specific damaging agents, corticoids and corticotrophins It is also noteworthy that some investigators claim to have found a rise in the renin content of the systematic blood during eclampsia The possibility should therefore be considered that eclampsia represents a disease of adaptation due to derailment of the defense mechanism against the developing embryo and placenta

"Accidental Thymus Involution." — Accidental thymus involution is almost certainly due to an excessive corticoid hormone elaboration under stress. It occurs in infants exposed to a variety of non-specific damaging stimuli and is histologically similar to that produced in experimental animals by stress, hypophyseal extracts or corticoids

Appendicitis. — It has already been mentioned that appendicitis-like changes may be produced by exposure to very severe alarming agents The appendix contains a great deal of lymphatic tissue and as we have repeatedly stated, the lymphatic organs are particularly sensitive to non-specific damage because the corticoids, liberated during the general-adaptation-syndrome, cause lymphocyte disintegration The invasion by intestinal microorganisms may be purely secondary. The occasional development of appendicitis as a complication of various acute systemic diseases may perhaps be explained on this basis

Tonsillitis. — The acute tonsillitis which often occurs after exposure to cold, following burns, radiation damage and other non-specific injuries, may perhaps also find its explanation in a similar phenomenon It is quite conceivable that this lymphatic organ also undergoes acute disintegration as a result of a defensive corticoid-hormone over-production and that microorganisms settle secondarily within the damaged lymphatic tissue, because the latter represents a particularly favorable medium for microbial proliferation





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creased pressor-substance formation would result from causes inherent in the kidney itself. This is not unexpected since hyperactivity of the pituitary-adrenal-kidney mechanism at any link of the chain could lead to essentially similar end-results.

Conclusions. — Much further work is required to elucidate the complexities of the diseases of adaptation. In the foregoing paragraphs, we have only attempted to give a general outline of this problem, since it is potentially of great importance not only for endocrinology, but for medicine as a whole. If the concept of the "Diseases of Adaptation" should prove to be correct, we would have to conclude that endocrine derangements play a crucial rôle in the major, fatal syndromes of internal medicine.

At first, it is difficult to understand why a single mechanism — namely, increased corticoid hormone production — should lead to such a variety of apparently unrelated diseases. Hereditary predisposition, a "locus minoris resistantiae" in one or the other target organ, the diet, etc., are all likely to influence the response of the various organ-systems in any particular individual. Even in experimental animals treated with pure desoxycorticosterone, renal lesions will be prominent in one case, heart lesions in another, etc. At the time when the etiology of tuberculosis was not known, it appeared very improbable that a single microorganism could produce seemingly so diverse diseases as Pott's disease of the bones, phthisis of the lungs, lupus of the skin, etc. Yet it is now a generally accepted fact that all these maladies are due to the tuberculosis bacillus.

It may be argued furthermore, that nature is not likely to provide a defensive mechanism which eventually defeats its own purpose. Yet, serum sickness and anaphylactic reactions are excellent examples of essentially useful defensive phenomena which can "derail" and then cause death. Even in endocrinology we could mention similar instances. Renal rickets is a bone lesion caused by excess parathyroid-hormone secretion in children with severe renal disease. In these, the insufficiency of the kidney causes hyperphosphatemia and other metabolic disturbances which are combatted by a compensatory increase in parathyroid-hormone secretion to maintain life. However, the secondary consequences of this defensive hyperparathyroidism are detrimental, since they produce bone resorption and skeletal deformity.

The most important objection to our concept appears to be that continued exposure to stress (chronic infections, endogenous intoxications, etc.), does not regularly produce "diseases of adaptation." However, as stated above, the latter diseases are not part of the general-adaptation-syndrome to stress, but represent derailments of the latter during the phase of resistance. Apparently, under normal conditions, increased corticotrophin production is accompanied by such metabolic changes which prevent the toxicity of the hormone, just as low-portein, low-sodium diets or acidifying salts prevent them. The diseases of adaptation can only ensue, therefore, if metabolic conditions are favorable for the manifestation of hypercorticoidism.

It is estimated on the basis of reliable statistics that approximately 50% of the total population of the United States will die from one or the other of the diseases of adaptation, especially those accompanied by hypertension or nephrosclerosis. Since the previously so important infectious diseases are now largely under control (thanks to progress in research on antibiotics) even greater stress will have to be placed in the future upon the diseases of adaptation, and the "wear-and-tear maladies" of aging.

The following PRELIMINARY CLASSIFICATION may help to survey the possible clinical implications of the General-adaptation-syndrome theory.

Gout. — Attacks of gouty arthritis notoriously tend to occur shortly after exposure to some stress. They are accompanied by hyperuricacidemia and deposition of uric acid "tophi" in joint and other cartilages. Recently it was found that, in predisposed patients, corticotrophin causes gouty arthritis, with similar changes in uric acid metabolism. Presumably stress exerts this effect via corticotrophin secretion.

Diabetes mellitus. — Firstly, corticotrophin raises the blood-sugar through the production of gluco-corticoids. Secondly, it increases endogenous uric-acid-production. Since several alloxan-like uric-acid-derivatives can cause diabetes due to Langerhans islet destruction, corticotrophin could conceivably produce diabetes through either of these actions. It is not known, however, whether a chronic increase in corticotrophin secretion, due to prolonged stress, actually is of importance in the pathogenesis of clinical diabetes.

Cushing's Syndrome. — Cushing's syndrome bears a striking resemblance to the experimental diseases of adaptation. It is usually accompanied by proliferation of basophils in the pituitary, increased development and hormone production of the adrenal cortex, hypertension and nephrosclerosis. Even cases of "acute Cushing's Syndrome," with generalized arteritis, have been described. It appears that Cushing's disease due to anterior-lobe tumors, or Cushing's Syndrome caused by adrenal-cortical hyperplasia are "*primary diseases of adaptation,*" not elicited by stress, but by a primary, often neoplastic, proliferation of those same tissues (anterior-lobe and adrenal) whose secondary over-activity is otherwise stimulated by exposure to non-specific damage.

Secondary Shock. — As previously stated, secondary shock is a condition in which excessive amounts of corticoids must be produced in order to maintain life. Thus it creates a condition of relative adrenal-insufficiency unless a compensatory corticoid overproduction can adequately meet the increased demands.

Shock is not produced by corticotrophin or corticoid hormone intoxication nor is it prevented by adrenalectomy; on the contrary, the greater the adrenal insufficiency, the more readily is shock elicited by non-specific stress. The condition thus appears to be *due to lack of defensive corticoid production* and thus differs from all lesions previously mentioned.

Gastrointestinal Ulcers. — The acute gastric erosions and duodenal ulcers (Curling's ulcer), which often develop in conjunction with adrenal hemorrhages, after extensive burns or particularly acute infections and intoxications, almost certainly also belong to this group. They cannot be produced by corticoid or corticotrophin overdosage nor are they prevented by adrenalectomy. Adrenalectomy or inactivation of the adrenals by hypophysectomy actually sensitizes the organism to the production of such ulcers. It appears therefore that here, as in the case of shock, we are dealing with a disease due to the insufficiency of adaptive mechanisms. The relationship between these acute gastrointestinal ulcers and the chronic peptic ulcer of man has not yet been clarified.

Addison's Disease and Simmonds' Disease. — Destruction of the pituitary or the adrenals greatly decreases resistance and is rarely seen in patients with hypertension and nephrosclerosis. These spontaneous maladies are equivalent to the derangements in the defence mechanism caused by adrenalectomy and hypophysectomy respectively. They can be regarded as *primary diseases of the adaptive mechanism,* in this sense they would be the counterparts of Cushing's disease, which leads to an aimless hyperactivity of the hormonal defense system.

Primary Renal Disease. — Undoubtedly in some instances hypertension and vascular lesions are caused by primary diseases of the kidney such as compression of renal tissue, partial constriction of the main renal arteries, inflammations, tumors, etc. However, local conditions in the kidney rarely produce a severe decrease in the intraglomerular blood pressure and hence they are uncommon causes of hypertension. When they occur, they could be regarded as another type of a primary hyperfunctional disease of the adaptive mechanism. In this case, in-

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DISEASES OF ADAPTATION DUE TO ENDOCRINE DISTURBANCES

I HYPERFUNCTIONAL.
- A PRIMARY DISEASES OF ENDOCRINES WHICH PARTICIPATE IN THE GENERAL-ADAPTATION-SYNDROME.
  - (1) Cushing's Disease [Pituitary hyperfunction]
  - (2) Adrenal tumors with "Cushing's Syndrome" [Adrenal-cortical hyperfunction].
  - (3) Chromaffinomas [Adrenal-medullary hyperfunction]
  - (4) Coarctation of the renal artery and other primary diseases of the kidney conducive to hypertension [Renal hyperfunction (hormonal)].
- B SECONDARY DISEASES DUE TO EXCESSIVE (OR ABNORMAL) RESPONSE OF ENDOCRINES TO STRESS
  - (1) Some types of hypertension
  - (2) Periarteritis nodosa (also arteriosclerosis and other vascular lesions ?)
  - (3) Nephrosclerosis
  - (4) Some types of nephritis (?).
  - (5) Rheumatic diseases (?)
  - (6) Waterhouse-Friedrichsen Syndrome.
  - (7) Eclampsia (?).
  - (8) Accidental thymus-involution.
  - (9) Some types of appendicitis (?).
  - (10) Some types of tonsillitis (?).
  - (11) Gouty arthritis (?).
  - (12) Some types of diabetes.

II HYPOFUNCTIONAL
- A PRIMARY DISEASES OF ENDOCRINES WHICH PARTICIPATE IN THE GENERAL-ADAPTATION-SYNDROME:
  - (1) Simmond's Disease [Pituitary hypofunction].
  - (2) Addison's Disease ["Status thymico-lymphaticus" (?). Adrenal-cortical hypofunction].
- B SECONDARY DISEASES DUE TO INSUFFICIENT RESPONSE OF ENDOCRINES TO STRESS.
  - (1) Secondary shock [Relative hypocorticoidism (?)].
  - (2) Acute gastrointestinal erosions ['Curling's ulcer"]

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Proceedings of a conference (61 pages, 24 figures, few references) concerning the relationship between Cushing's syndrome and the general-adaptation-syndrome.

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A most interestingly written book (333 pages, 40 figures, numerous references) in which the author discusses his life-work on homeostasis" Chief emphasis is placed upon the sympathetic nervous system and the adrenal medulla as regulators of the adaptive mechanism

EPPINGER, H · *Die Permeabilitatspathologie* Springer-Verlag, Wien (1949)

A monograph (755 pages, 145 figures (many in colour), 65 tables, numerous references) discussing the concept that diverse noxious agents can cause a syndrome of serous inflammation", characterized by the entrance of plasma into the intercellular spaces and even the cytoplasm of parenchymatous cells The author finds that in stress situations, K and PO_4 leave the cell while Ca, Na Cl and blood-plasma enter Thus, the chemical composition of cell and plasma tend to become equalized, presumably as a result of increased membrane permeability This may explain the retention of sodium and hyalin-like protein material in damaged cell (e g, heart, vessels, kidney, brain) and thus suggests interesting relationships to the 'diseases of adaptation'. (In German)

FLOSI, A Z *Reacão de Alarme e o Sindrome General de Adaptacão* Conceito de Doenças de Adaptação Importância Clinica e Cirurgica

A survey (29 pages, 10 figures, 29 references) concerning the general-adaptation-syndrome and the diseases of adaptation. The author's personal investigations concerning suprarenal insufficiency in malaria are of particular interest (In Portugese)

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PLURIGLANDULAR INSUFFICIENCY AND ALLIED CONDITIONS

Since the various glands which constitute the endocrine system are largely dependent upon each other, it is evident that a primary disease of one gland may entail secondary derangements in other endocrines. This is especially true of the anterior-hypophysis, which through its various trophic hormones regulates the function of so many other glands of internal secretion.

The name PLURIGLANDULAR INSUFFICIENCY ("insuffisance pluriglandulaire endocrinienne") was given by *Claude and Gougerot* in 1907 to a peculiar disease entity characterized by simultaneous insufficiency of various endocrine organs, especially the hypophysis thyroid, adrenal and gonads.

The retardation in general somatic development occasioned by various types of chronic stress (chronic infections, malnutrition, etc.,) likewise exerts an adverse affect upon the function of the endocrines, it tends to cause both sexual and somatic infantilism, if it develops at an early age, or cachexia similar to that seen in Simmond's disease if it commences later.

In view of contemporary knowledge it seems probable that most of the cases of so-called pluriglandular insufficiency were actually special types of anterior-lobe failure. In some instances a primary atrophy or destruction of the anterior-lobe could have led to the involution of other endocrine glands, which depend upon pituitary trophic hormones; here the only noteworthy features in the clinical course were the disproportionate prominence of thyroid, adrenal or gonadal insufficiency symptoms. Hypothyroidism and hypocorticoidism are usually not as conspicuous, even in severe anterior-lobe failure, as with isolated destruction of the thyroids or adrenals respectively, yet in some types of pituitary dwarfism and Simmond's disease, hypothyroidism and hypocorticoidism can be prominent. Hence, in such instances it is unnecessary to speak of a special pluriglandular insufficiency syndrome.

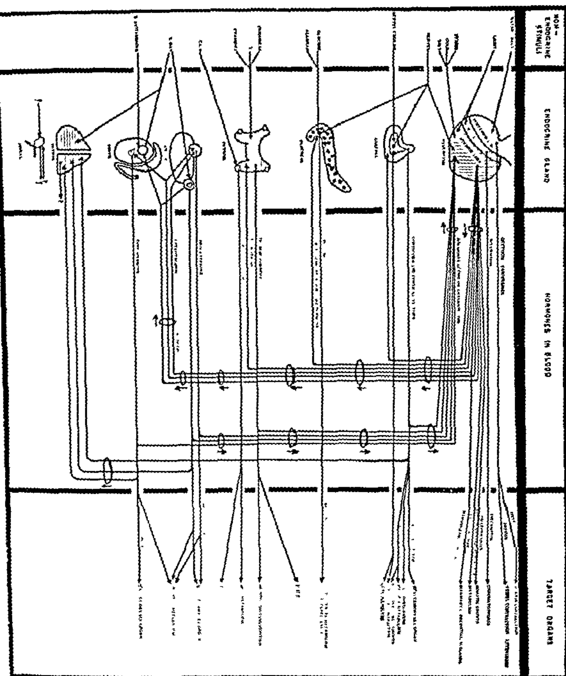
In 1910 *Falta* in Vienna described a syndrome under the name "MULTIPLE ENDOCRINE GLAND SCLEROSIS" ("Multiple Blutdrusensklerose") which he defined as a disease caused by the simultaneous sclerosis and atrophy of several endocrine glands. Most frequently affected were the hypophysis, thyroid, adrenals and gonads, more rarely the parathyroids. The condition was ascribed to some unknown infection, which would tend to affect these glands selectively. The author even felt that perhaps the term "multiple endocrine gland inflammation" would be more appropriate.

It is probable that in many of Falta's cases the patients merely suffered from various special types of Simmond's disease. The so-called "primary atrophy" of endocrine glands (especially of the adrenals, thyroids and hypophysis) which is so often preceded by some acute type of stress (e.g., difficult deliveries, intoxications infectious diseases) as well as the inflammatory atrophy of the gonads (e.g., in mumps) suggest, however, that the possibility of direct infections, or toxic damage of several members of the endocrine system should not be ruled out.

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GENERAL SURVEY OF HORMONAL CORRELATIONS

In this last chapter we shall attempt to present a brief synopsis of the salient factors regulating and coordinating the function of the endocrine glands

As indicated in the adjacent table the endocrines are governed both by hormonal and by non-endocrine stimuli, the former arrive to them exclusively through the blood, the latter either through the blood or through nervous pathways

As a source of hormones which influence endocrine glands the ANTERIOR-PITUITARY occupies an especially out-

standing position. It produces trophic hormones which stimulate the adrenal cortex (corticotrophin), the pancreas (diabetogenic hormone), the thyroid (thyrotrophin), the ovaries and the testes (luteotrophin, LH and FSH).

Only few non-endocrine target organs are directly affected by anterior-lobe hormones, these are: the mammary glands (growth stimulated by mammogenic hormone, secretion by luteotrophin), *somatic growth in general* (stimulated by somatotrophin), the development of the preputial glands and certain metabolic processes (stimulated by anterior-lobe hormones whose nature has not yet been fully elucidated)

Most of the effects of the anterior-lobe upon non-endocrine target organs are mediated by other endocrine glands. Thus under the influence of corticotrophin the *adrenal cortex* produces corticoids and cortical testoids, which act upon the accessory sex organs, gluconeogenesis, mineral metabolism, blood pressure, smooth-muscle contraction, the thymus and other lymphatic organs.

The diabetogenic hormone influences carbohydrate metabolism, at least partly, through its effect upon the insulin production of the *pancreas*

Thyrotrophin acts upon the B.M.R., other metabolic processes, growth and differentiation, through the intermediary of the thyroid-hormone which it causes to be produced in the *thyroid*

Gonadotrophin influences the accessory sex organs, growth and metabolism by causing the *ovary* and *testis* to produce sex hormones (progesterone, estradiol, and testosterone)

Conversely, the hormones produced by the adrenal cortex, pancreas, thyroid and gonads act back upon the anterior-lobe. Thus by inhibiting the formation of the corresponding trophic hormones (through the "compensatory atrophy and compensatory hypertrophy mechanism") they help to maintain their own hormone production at a normal level.

Light, stress (especially cold), *dietary factors and nervous stimuli are the most important non-endocrine factors which influence the production of anterior-lobe hormones.* Thus the anterior-lobe of the hypophysis occupies a central position in the endocrine system and is the chief coordinator which adjusts the function of the endocrines to variations in hormone requirements, conditioned by changes in the internal or external medium of the body.

The POSTERIOR-LOBE produces only directly acting hormones, namely, oxytocin which influences uterine contractions and vasopressin, which affects blood-vessel contraction and diuresis. Its cells are not significantly influenced by hormonal stimuli, but are very responsive to variations in water and salt metabolism which probably affect its vasopressin production through the intermediary of the nervous system.

The MIDDLE-LOBE of the pituitary produces intermedin which acts directly upon the chromatophores. Its cells are *influenced mainly by light* which affects them through the intermediary of the nervous system.

The ADRENAL CORTEX receives no important direct stimuli, all the numerous factors which affect its development and function, reach it through the intermediary of the anterior-lobe whose *corticotrophin is the only important* regulator of adrenal-cortical activity.

The ADRENAL MEDULLA produces adrenaline which affects the blood pressure, smooth-muscle contractions and glycogenolysis. The medulla, unlike the cortex, does not respond to pituitary trophic stimuli and indeed is almost *entirely refractory* to all types of stimulation except those which reach it through its cholinergic, sympathetic (secretory) nerves. Direct injection of acetylcholine, the humoral mediator of these nerves, also causes the medulla to discharge adrenaline.

The PANCREAS produces *insulin* which acts directly upon carbohydrate metabolism The function of the Langerhans islets is *largely dependent*

upon: diabetogenic and (other?) anterior-lobe hormones, nervous impulses which reach it through the vagus, the glucose concentration of the blood and certain drugs (such as alloxan) which exert a specific toxic effect upon islet tissue.

The THYROID appears to produce only *one kind of hormone; it acts directly* upon its target organs. The elaboration *of this thyroid hormone is stimulated* by the thyrotrophin of the anterior-lobe, but certain drugs — e.g., thiourea derivatives, iodine and cyanides — also exert a direct effect upon the thyroid and its hormone production. The thioureas appear to inhibit the synthesis of thyroid hormone. Iodine is an essential constituent part of this endocrine principle and hence necessary for its synthesis; besides this, iodine appears to inhibit the effect of thyrotrophin upon the thyroid cells. The rôle of the cyanides is less clearly understood, but perhaps they create an increased demand for thyroid hormone due to their toxic effect upon enzyme systems necessary for normal metabolism, perhaps they merely prevent the entrance of iodine into the thyroid.

The PARATHYROIDS do not appear to receive any important trophic stimuli from the anterior-lobe or the nervous system, their function being largely regulated by the calcium and phosphate content of the blood. They appear to produce only one type of hormone, this acts upon calcium and phosphate metabolism through its influence upon the mineral stores of the skeleton and perhaps also through the renal elimination of calcium and phosphates.

The OVARY responds to pituitary FSH by the formation *of mature follicles*. The folliculoid-hormone production of the latter and their transformation into corpora lutea are under the influence of LH. The maintenance and progesterone formation of the corpora lutea on the other hand depend upon luteotrophin.

Most of the external stimuli affect the ovary through the intermediary of the anterior-lobe hormones, but X-rays exert a direct, destructive effect upon the female gonad. It is relevant (though not specifically indicated in the chart) that folliculoids also appear to exert direct effects upon the ovary (e.g., follicle *maturation in the earliest pre-antrum*-bearing stages, formation of "pregnancy-type" *corpora lutea in synergy* with luteotrophin).

In the TESTIS FSH *stimulates spermatogenesis* while LH increases the size, number and *hormone production of the* Leydig cells. Testosterone is the only important testis hormone known at the present time. The possible hormonal nature of the highly spermatogenic, but non-testoid, Δ^5-pregnenolone must also be considered. Like the ovary, the testis responds to external stimuli mainly through the intermediary of the anterior-lobe, although X-rays and vitamin-E deficiency appear to exert a direct, destructive influence upon it.

The THYMUS undergoes atrophy under the influence of corticoids, folliculoids and testoids, probably most steroid hormones exert a similar, though less pronounced, effect upon thymocytes. It is still doubtful whether the anterior-lobe exerts any direct effect upon the thymus, other than that mediated by the steroid-producing glands. Yet, somatotrophin appears to be thymotrophic.

In spite of the extraordinary sensitivity of thymus tissue to any type of change in the external or internal environment, only very few agents are known to affect it directly, that is, without the mediation of the steroid produc*ing glands. The thymus is not known* to produce any true hormonal principle.

On morphologic grounds the PINEAL is often classified among the endocrines, *but no definite data are available, either* concerning the hormones which it might *produce, or the stimuli which influence* its development and function.

INDEX

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To facilitate the use of this index block numerals [e g , **12**] refer to principal discussions of a subject bracketed numerals [e g (12)] to illustrations and ordinary roman numerals, [e g , 12] to all other parts of the text.

Greek letters (e g , α, β γ δ Δ) numbers which form part of indexed words and short connecting words (e g in, the, of, for from to as) are neglected in determining the alphabetic position of entries in this index

When a "target organ" A is influenced by a stimulus B, this is indicated by an arrow pointing from B to A thus B → A, instead of the usual cumbersome entry, "A, effect of B upon'; conversely the effect of A upon B is indicated by the entry B ← A, while a general discussion of the interrelation between A and B is indexed thus A ⇆ B

Generally the effect of hormones upon target organs is studied comparatively in intact and hormone deficient animals hence the effects of overdosage with hormones and of extirpation of the gland which produces them are listed conjointly under the gland s name Thus the effects upon the kidney of hypophyseal extracts and of hypophysectomy are indexed conjointly under the heading "Hypophysis → kidney" On the other hand the effect of endocrine diseases upon the kidney would be listed separately, e g "anterior-lobe hypofunction → kidney , since here we are dealing with fundamentally different clinical observations

Such terms as hyperthyroidism, hypocorticoidism, etc , which designate excessive or subnormal function of a gland are used to denote the corresponding clinical conditions (diseases) not the experimental counterpart (induced by hormone administration or elimination of a gland)

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